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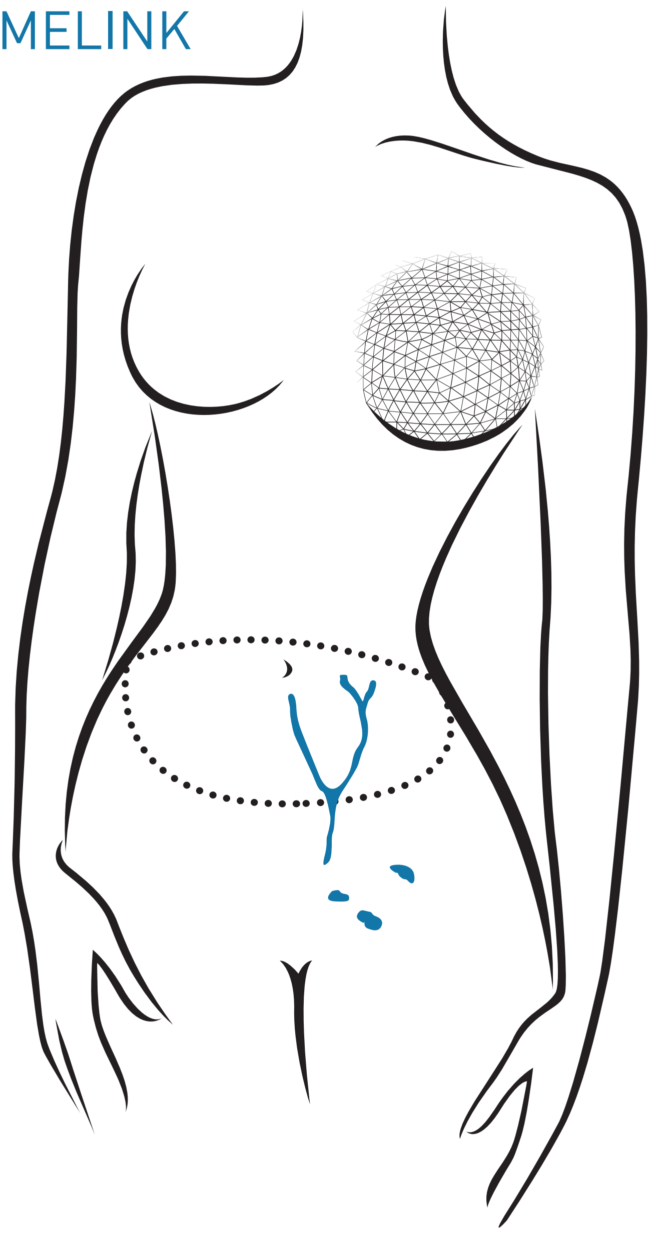
# TECHNICAL INNOVATIONS IN AUTOLOGOUS BREAST RECONSTRUCTIONS

STEFAN HUMMELINK



# STELLINGEN

1. Het is mogelijk om een autologe borstreconstructie driedimensionaal te plannen op basis van preoperatieve beeldvorming. (dit proefschrift)

2. Het is mogelijk om een patiëntspecifieke driedimensionale virtuele planning van de borstreconstructie te projecteren op de patiënt. (dit proefschrift)

3. Door deze projectie methode worden anatomische structuren en hulplijnen ten behoeve van de autologe borstreconstructie correct weergegeven. (dit proefschrift)

4. Door deze projectie methode worden meer perforerende bloedvaten correct geïdentificeerd dan met de conventionele preoperatieve plan methode. (dit proefschrift)

5. Door deze projectie methode kan een DIEP lap borstreconstructie sneller worden uitgevoerd dan met de conventionele preoperatieve plan methode. (dit proefschrift)

6. "There's a way to do it better - find it". (Thomas Edison)

7. "By failing to prepare, you are preparing to fail". (Benjamin Franklin)

8. Als ge 't nie mir wit, dan vatte kit. Kékt ge ur nog tusse dur, dan vatte pur. (klustip)

# TECHNISCHE INNOVATIES BIJ AUTOLOGE BORSTRECONSTRUCTIES

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# TECHNISCHE INNOVATIES BIJ AUTOLOGE BORSTRECONSTRUCTIES

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*Voor mijn ouders*

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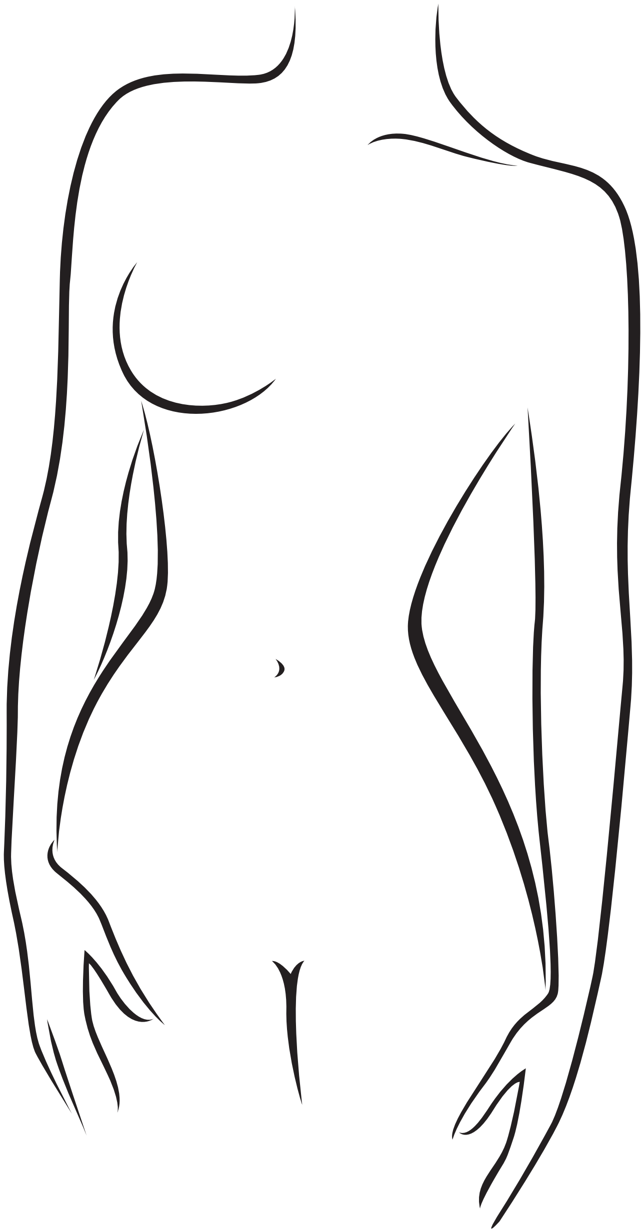
# CHAPTER 1

## Introduction, aims and outline of the thesis



**Breast cancer** was described by the ancient Egyptians as far back as 3000 B.C. and 1500 B.C. in the "Edwin Smith" and "George Ebers" papyruses, respectively. In its medical recommendations for cancer, or the "tumor against the god Xenus", it stated that "do thou nothing there against".[1] Fortunately, the improved understanding of human anatomy in the 18th and 19th centuries led to the first successful breast cancer surgical operations. The first surgical removal of the whole breast, was developed in 1889 by William Stewart Halsted and became the standard treatment for breast cancer up until the 1970s.[2] The less invasive method of partial removal of the breast, or lumpectomy, was found to be as effective as total mastectomy for the treatment of invasive breast cancer after evaluation in clinical trials. [3]

Nowadays, annually over 14,000 women in the Netherlands are diagnosed with breast cancer and are often forced to have one or both breasts surgically removed in order to treat the disease.[4] Despite continuous research and earlier detection of breast cancer, surgical procedures such as mastectomy or lumpectomy remain an important technique to adequately treat the disease. During this procedure, axillary lymph node dissection (**lymphadenectomy**) may be performed to evaluate for metastases.

Preventive ablation of the breasts is frequently chosen in case of a high-risk BRCA1 or BRCA2 gene mutation, a tumor suppressor gene. These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60–80% in those affected.[5] The decision to willingly have both breasts removed weighs heavily on the psyche of the genetically predisposed woman. Options are however available for recreating the removed breast, either in a direct or delayed setting.

The aim of a **breast reconstruction** is to restore the appearance of a natural breast. In the case of unilateral reconstruction, the reconstructed breast should match the remaining contralateral breast in size, shape and position. After partial or complete removal of the breast, reconstructions can be performed immediately, or years after the procedure. The new breast shape can be created using an implant and/or the patient's own, autologous, tissue from another part of the body.

The first autologous breast 'reconstruction' dates back to 1895, when a fist-sized lipoma was transplanted from the patient's flank to the torso.[6] The first musculocutaneous flap was introduced by Tansini in 1906, utilizing the latissimus dorsi muscle.[7] Six years later, the first latissimus dorsi (**LD**) muscle flap was used by d'Este for covering up a mastectomy defect.[8] The back muscle along with its skin paddle is elevated, and rotated to anterior in order to cover up the mastectomy defect.

A new era in breast reconstructions dawned when the first silicone implant was used in 1963.[9] This method of reconstruction became widely accepted, after previous disastrous attempts using paraffin or silicone injections. [10] Tissue expanders were also introduced in order to stretch the skin and pectoral muscle so larger implants could be used to match the patient's contralateral breast. Nowadays, many breast reconstructions are conducted using implants. As is the case with any foreign object being inserted into the human body, it is the body's natural reaction to create a capsule around the implant, issued by the immune response. This collagen-fibre capsule can contract over time, leading to a discomforting and aesthetically distorted breast reconstruction. Furthermore, although modern-day implants have improved in safety, the risk of implant rupture increases with its age. Between the third and tenth year after implantation, a minimum of 15% of modern implants can be expected to rupture.[11, 12] From an aesthetical viewpoint; more natural result is obtained through autologous breast reconstruction.[13] Therefore the concept of autologous breast reconstruction is considered favorable.

In the late 1970s, autologous breast reconstruction was rediscovered by Schneider and Olivari who adapted the LD flap for reshaping a breast after mastectomy and radiation therapy. [14, 15] In 1982, the first free transverse rectus abdominis myocutaneous (**TRAM**) flap was transferred to the torso. [16] In such free flap transfer, the tissue is completely detached from the donor site and transplanted to the new location. The supplying blood vessels from the free flap are reattached at the recipient's artery and vein in order to restore circulation. Depending on the diameter of the blood vessels, a microscope may be used to aid in the anastomosis of the artery and vein. The TRAM flap technique uses the lower abdominal skin and subcutaneous tissue including muscle for the reconstructed breast. Either the internal mammary or thoracodorsal vessel is used as recipient vessels for the free TRAM flap, depending on diameter of the harvested vessel. Since the TRAM flap technique can mean removal of a part of transverse rectus abdominis muscle, this may lead to weakness of the abdominal wall and susceptibility to herniation. The search for a reconstruction technique without the latter risk led to the development of a free flap without the added morbidity of sacrificing an important muscle. The hypothesis that a lower abdominal flap solely perforated by a periumbilical vessel could be used, was confirmed in 1989 when two cases were published by Koshima describing the repair of skin defects using "inferior epigastric skin flaps without rectus abdominis muscle".[17] A few years later, in 1992, Allen and Treece reported on the usage of the deep inferior epigastric artery perforator (**DIEP**) flap for breast reconstruction.[18] The vascularization of the harvested flap, consisting of only abdominal adipose tissue and skin, relies on the deep inferior epigastric artery and its perforators. A **perforator** emerges from the deep vascular network and pierces a muscle to vascularize superficial structures, measuring in general approximately 2 mm in diameter and is randomly distributed. The ability to separate these miniature vessels from the rectus abdominis muscle raised the procedure to a higher level of technical refinement in breast reconstruction, setting a new standard in muscle-sparing free flap transfers.

Following the innovative principles of a DIEP flap, other perforator flaps from various donor sites were proposed for usage in breast reconstruction. [19-23] The superior or inferior gluteal artery perforator (**S-** or **I-GAP**) flap is harvested from the buttocks. Flaps from the thigh, such as the transverse musculocutaneous gracilis (**TMG**) flap and the transverse upper gracilis (**TUG**) flap incorporate muscle into the flap. With available reconstructions continuously being refined, the TUG flap was further developed into the profunda artery perforator (**PAP**) flap, where no gracilis muscle is harvested for reconstruction. Further elaboration on the DIEP flap gave rise to the superficial inferior epigastric artery perforator (**SIEA**) flap, where flap vascularization depends on only the superficial arterial network, leaving out the necessity of incising the abdominal muscle for access to the deep inferior artery.

The DIEP flap, nowadays the workhorse of free flap breast reconstructions, continues to evolve. In cases of insufficient donor volume to match the contralateral breast, it was proposed by DellaCroce et al. to stack DIEP flaps. [24] Both the patient's ipsi- and contralateral DIEP flaps are layered on top of each other, microsurgically linking the blood supply of both flaps prior to anastomosis of the recipient internal mammary vessels.

New innovative approaches such as incorporating lymph nodes in the DIEP flap for treating lymphedema of the arm associated with lymphadenectomy was introduced by Saaristo et al.[25] Through such autologous lymph node transfer (**ALNT**), lymphedema of the arm may be reduced, as first discovered by Becker et al.[26] In this more elaborate breast reconstruction procedure, the DIEP flap is harvested along with inguinal lymph nodes, which will be positioned in the axilla to aid in the lymphatic drainage.

Surgeons are constantly pushing the limits of breast reconstructive techniques. With increasing levels of expertise required, assistance on a technical level is well received.

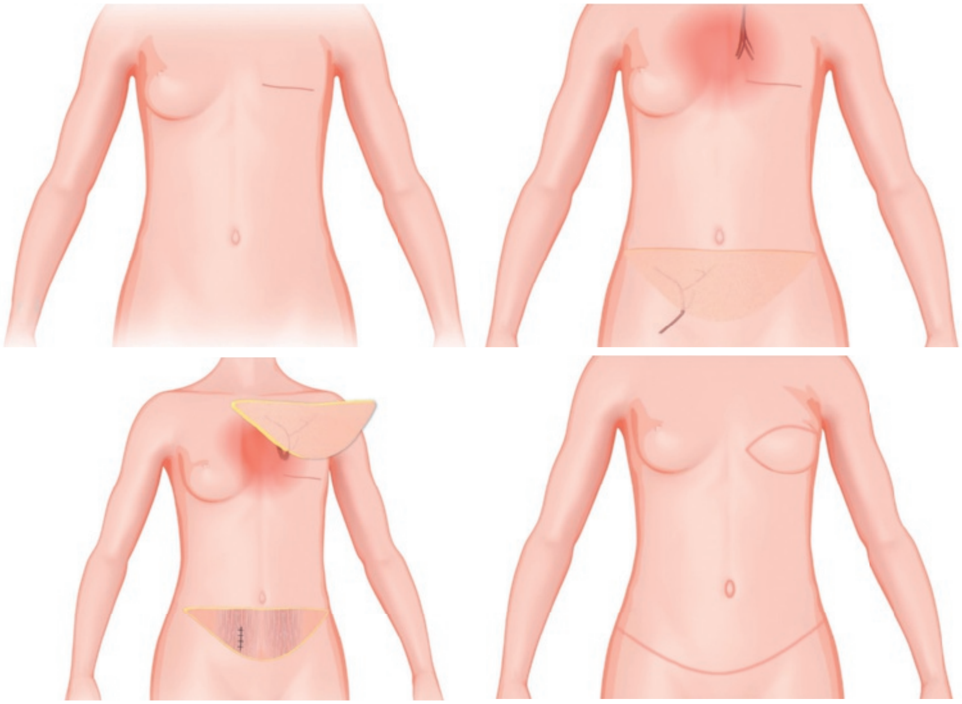


**Figure 1:** The deep inferior epigastric artery perforator (DIEP) flap is harvested from the abdomen and trimmed into a breast shape. The deep inferior epigastric artery is anastomosed at the internal mammary artery to restore blood supply to the flap.

## Technological aspects in breast reconstruction

Simultaneous to the clinical advances in breast reconstruction, progress has been made on the technological level. Vice versa, various imaging techniques found their footing in the area of breast reconstruction.

Computed tomography (CT) has undergone major improvements since its invention in 1972 by Godfrey Hounsfield. [27] Where the first generation CT scanners produced an image taking about five minutes to complete and could only image the patient's head, nowadays, patients can be scanned from head to toe within 3 seconds at resolutions well under a millimeter. When injected with a contrast agent, blood vessels can be depicted using computed tomography angiography (**CTA**) within half of a second, with image resolutions of under 0.5 mm. Therefore, this imaging modality is more than capable of depicting small blood vessels and in particular, perforators. Although other methods are available to locate perforators, such as color Doppler (duplex), hand-held Doppler ultrasound (US) and Magnetic Resonance Angiography (MRA), CTA currently remains as the gold standard in preoperative imaging for autologous breast reconstructions. [28-33]

The concept 3-dimensional stereophotogrammetry (**3D photography**) was adopted into medical imaging in the 1990's, mainly for facial morphology. [34] By simultaneously obtaining two images under two different angles, indicating landmarks such as the exocanthion (lateral corner eye), cheilion (outermost corner of the mouth) and pronasale (nasal tip), a 3D representation of a patient's face could be calculated. When computing power increased over the years, more surface features could be considered, improving accuracy and calculation times of 3D photography. Through this advancement, 3D imaging method became available for breast reconstructive purposes (figure 2). Consecutive validation studies showed the method to be able to accurately determine breast shape and volume. [35, 36]

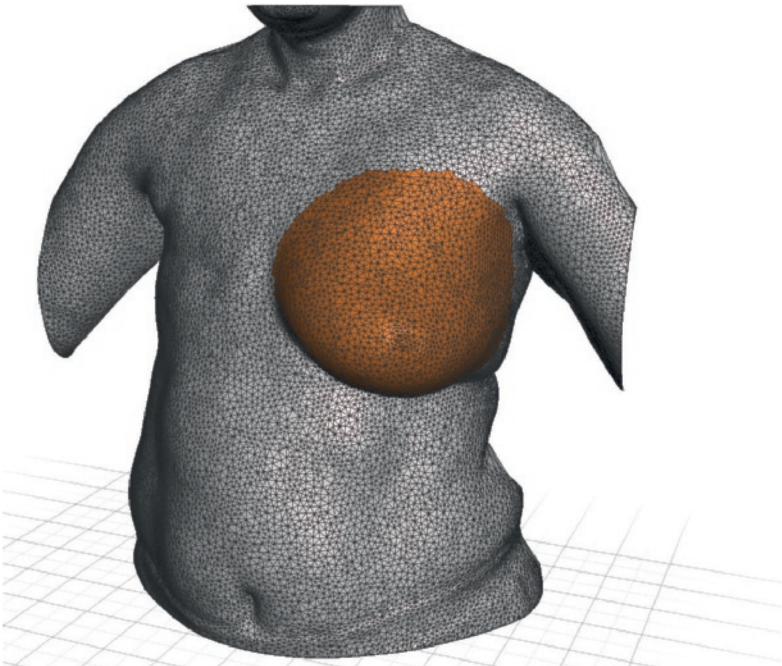


**Figure 2:** A virtual model of an unilateral breast reconstruction patient obtained through 3D-stereophotogrammetry. The breast of the unaffected contralateral side (indicated in orange) is used for volume calculations.

Current protocols in our hospital dictate that all breast reconstruction patients have 3D photos taken for clinical documentation and CTA scans performed for detecting the randomly distributed perforators, vascular assessment and to rule out any contra-indications. These techniques facilitate the possibility of pre-operative procedure planning, supporting surgeons in decision making and patient selection. In such **virtual 3D planning** the breast reconstruction is pre-operatively designed utilizing all available imaging data to gain pre-operative knowledge in vascular and lymphatic anatomy, and quantifying adipose tissue (figure 3). Making full use of these techniques led to the development of the innovative approaches covered by this thesis, particularly how to create and transfer this virtual 3D planning towards the patient.

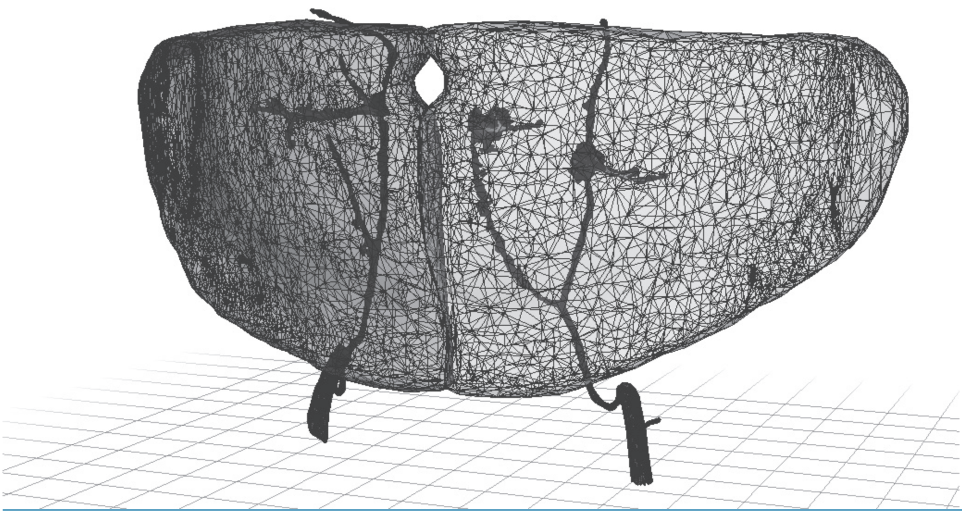


**Figure 3:** 3D planned DIEP flap for a bilateral breast reconstruction without lymph node transplantation based on CTA. The 3D reconstruction indicates the total flap size and relevant blood vessels.

## AIMS OF THE THESIS

The research as presented in this thesis aims to improve the outcome of autologous breast reconstructions. Understanding the patient-specific anatomy of blood vessels, in particular perforators at the donor site, and breast volume and shape prior to surgery can be beneficial in improving autologous breast reconstructions. As technology has vastly improved over the last years, it was investigated whether new techniques were available to aid autologous flap survival and breast reconstruction success.

At the beginning of this research, it was found that the imaging modalities provide sufficient quality to depict and highlight perforators, and this computed tomography angiography data could be processed further on a workstation. The encountered problem of having this information only available on a computer monitor, and not on the patient, led to question whether this gap could be bridged. A method of displaying the highlighted perforators onto the patient's skin through a video projector was proposed, with positive pilot study results. However, the rudimentary set-up needed further improvement in terms of usability and accuracy. Through means of early health technology assessment, insight was gained in the economical benefits using this projection technique, which in term justified future development costs. To fully understand the added value of the innovation, the aim was to validate the new prototype and its impact on DIEP flap breast reconstruction surgery. Finally, future possibilities with the new innovative projection method and 3D printing were explored, aiming to aid the surgeon in localizing anatomical structures and obtaining the correct breast volume and shape.

## OUTLINE OF THE THESIS

All studies presented in this thesis were performed within the Radboud Institute for Health Sciences at Radboud university medical center Nijmegen at the Department of Plastic Surgery in collaboration with Department of Radiology & Nuclear Medicine and the 3D laboratory associated with the Department of Oral & Maxillofacial surgery.

**Chapter 2** describes the initial pilot study to investigate the feasibility of preoperatively creating patient-specific DIEP flap planning and projecting this onto the patient's lower abdomen using a hand-held mini projector.

After promising preliminary results, a cost-effectiveness study of the projection technique was conducted as presented in **chapter 3**. Through early health technology assessment, the financial impact was estimated to gain insight whether or not it was economically worthwhile to further develop this technique.

In order to assess the clinical impact of the innovative projection method, **chapter 4** describes a single-center randomized controlled trial. In this chapter, a newer version of the hand-held projector was validated by comparing the current standard of care to the projection method.

The research in **chapter 5** investigated whether or not it was feasible to indicate pre-operatively the location of inguinal lymph nodes for the usage in an autologous lymph node transfer flap alongside a DIEP flap breast reconstruction. Here, the virtual 3D planning for the DIEP flap was further refined and assessed for accuracy.

Elaborating on previous results, **chapter 6** describes preoperative breast and flap volume calculations, where total flap volumes were taken into account during the virtual planning in order to achieve symmetric breast volumes. The harvested flap weight was compared to the pre-operatively created virtual 3D planning after it was projected onto the patient's abdomen.

**Chapter 7** describes a method of aiding in the creation of the correct shape of the breast. By mirroring the unaffected breast in 3D, one was able to obtain the desirable shape for symmetric breast reconstructions. Using 3D printed templates, the harvested flap of a specified volume could be placed inside the mould in such a manner that the flap adopts its shape aiding in matching the reconstructed breast to the contralateral side.

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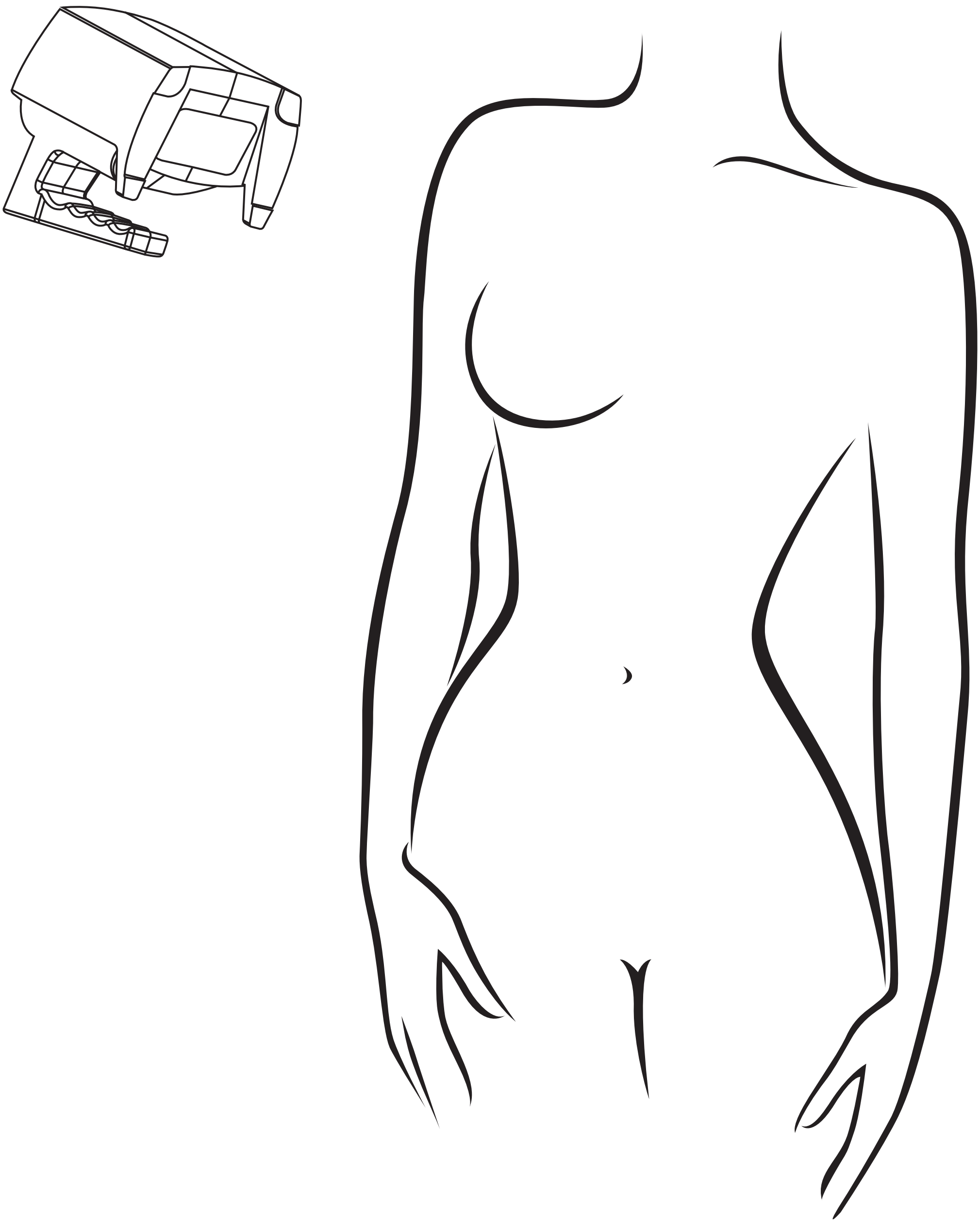
# CHAPTER 2

## Preliminary results using a newly developed projection method to visualize vascular anatomy prior to a DIEP flap breast reconstruction



## ABSTRACT

In a deep inferior epigastric perforator (DIEP) flap breast reconstruction, computed tomography angiography (CTA) is currently considered as the gold standard in preoperative imaging for this procedure. Unidirectional Doppler ultrasound (US) is frequently used; however, this method does not distinguish the main axial vessels from perforator arteries at the height of the fascia, it has a limited penetration depth, and it cannot assess the branching patterns of the deep inferior arteries. A new method and system were developed, which consisted of a video projector preoperatively displaying the location and intramuscular course of the artery perforators and subcutaneous branching on the patient's abdomen.

All patients ($n$ = 9) underwent a standard protocol: a preoperative CTA was performed and the DIEPs were localized using a unidirectional Doppler probe. In addition, a three-dimensional (3D) reconstruction of the perforator locations based on CTA was projected on the abdomen of the patients. All projected perforator locations were assessed using a unidirectional Doppler probe. The intraoperative results were collected for comparison.

A total of 88 locations were marked with the use of unidirectional Doppler and a total of 100 perforators were projected ($p$ = 0.38). In 98 out of 100 projected perforator locations, a Doppler signal was audible. The intraoperative results demonstrate that 19 out of 34 transplanted perforators were correctly identified with unidirectional Doppler (56.9% ± 31.4%), where the projection method properly revealed 29 locations (84.3% ± 25.8%) ($p$ = 0.030).

The projection method is not only capable of providing more information and identifying more perforators used for transplantation than unidirectional Doppler probing but also more accurate in pointing out the corresponding perforator found intraoperatively.

## INTRODUCTION

In a deep inferior epigastric perforator (DIEP) flap breast reconstruction, an elliptic flap of abdominal skin and subcutaneous fat is elevated from the rectus fascia, leaving the rectus abdominis muscle in situ and largely intact with only an incision through the supraumbilical portion. The flap is perfused by one or more deep inferior epigastric artery perforators, and the selection of these perforators is crucial to ensure the viability of the flap.

Computed tomography angiography (CTA) is currently considered as the gold standard in preoperative imaging for DIEP flaps due to its high accuracy and low interobserver variability.[1-7] This imaging modality has been shown to be more accurate than other imaging modalities for the DIEP flap planning. Unidirectional Doppler ultrasound (US) is currently used to scan the entire lower abdomen. However, this method does not distinguish the main axial vessels from perforator arteries at the height of the fascia, it cannot assess the branching patterns of the deep inferior arteries, and it has a limited penetration depth although essential for obese patients. [8, 9]

With the use of a video projector, the intramuscular course, perforating locations, and subcutaneous branching of the artery and perforators can be displayed preoperatively on the patient's abdomen, providing visual support. Only the marked perforators should be probed to ensure an accurate projection. This additional insight may lead to surgical benefits in DIEP flap breast reconstructions, including a reduced learning curve, a decrease in surgery time, an improved flap viability and thus patient safety, and decrease in operative stress. [7, 10-13]

In this technical report, our initial experiences with preoperative projections onto the patient's abdominal wall using a pico video projector are presented.

## MATERIALS AND METHODS

Between January and April 2014, a total of nine female patients were included for projecting CTA planning data prior to DIEP flap breast reconstruction. A waiver from the medical ethical committee was obtained and these patients followed a standard protocol: (1) Preoperative CTA was performed to determine the vascular quality and (2) the DIEPs were localized using a unidirectional Doppler probe. The only addition to this protocol was a preoperative projection on the abdomen of the patients, based on a three-dimensional (3D) reconstruction of the CTA. This projection was always performed after the perforator mapping to prevent bias. All projected perforator locations were assessed with Doppler US for a pulsating sound.

The coordinates of all significant perforators were intraoperatively collected prior to incision of the abdominal fascia and noted on a metric grid using the umbilicus as the reference point. These include accessory submillimetric perforators accompanying larger perforators. All measurements were taken at the height of the abdominal fascia. The coordinates of only the intraoperatively used perforators were reviewed for detection using unidirectional Doppler US and projection perforator locations within a 1-cm radius, for these have the highest clinical relevance.

Double-sided paired *t*-tests were performed for the number of perforator locations estimated using Doppler US and the projection method and to evaluate the ratio between the predicted perforator location and the transplanted perforator location. This test was also used to assess the distance between the Doppler US and the projected locations in relation to intraoperative perforator coordinates.

### 3D CTA reconstruction

Patients were scanned with a Toshiba Medical Systems Aquilion One 320 slice CT scanner (Toshiba Medical Systems, Tokyo, Japan). Using a VitreaAdvanced fX Workstation (Vital Images, Toshiba Medical Systems Group Company, Minnetonka, U.S.A), the abdominal vascular anatomy was reconstructed in 3D. The intramuscular trajectory of the deep inferior epigastric artery and its branches towards the perforators were highlighted in the Vitrea software. The umbilicus is indicated with a purple arrow and it represents the center of the 20 × 10-cm guidelines, essential for achieving a global orientation. All significant perforators (diameter >1 mm) were annotated with a yellow arrow, perpendicular to the CT table. The additional purple arrows indicate the most favorable perforators for transplantation. Consecutively, the 3D reconstruction is oriented from the anterior to posterior direction, displaying the annotation arrows as circles, as seen in figure 1.

### Projecting onto the patient

Preoperatively, the CT scan was performed with all patients in the supine position in bed. A handheld PicoPix PPX2480 Pico projector (Philips, Eindhoven, the Netherlands) was used to preoperatively display the previously described image onto the abdominal wall of the patient. Alignment of the purple circle corresponding with the umbilicus was achieved by moving the projector. The magnification of the image was corrected by altering the projector's height to match the predefined guidelines using a ruler. The rotation and skewing were removed by physical adjustments so the guidelines were projected horizontally and parallel to each other. The Doppler US markings and the subsequent projection are presented in figure 2.

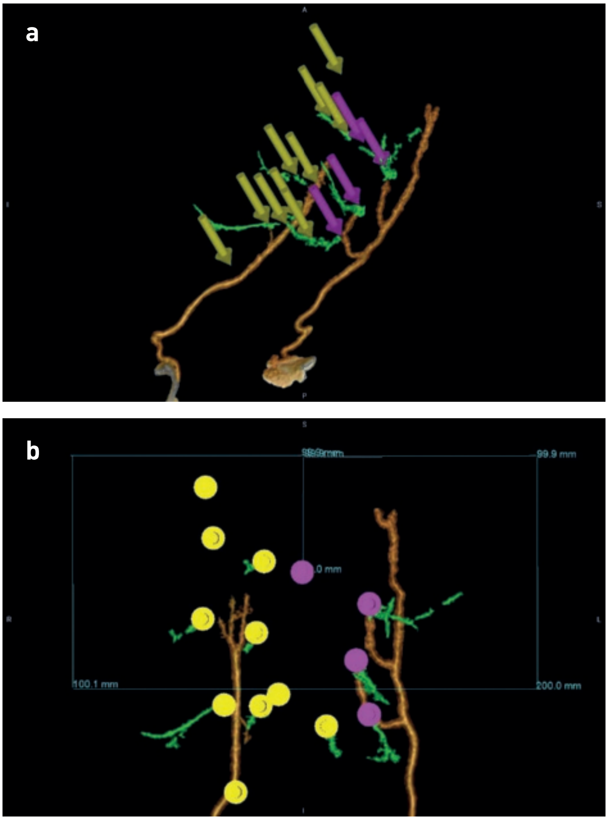



**Figure 1:** a) 3D reconstructed deep inferior epigastric artery and annotated perforators (yellow and purple arrows) with their subcutaneous branching pattern (green). b) Anterior-/posterior-oriented viewpoint with guidelines.

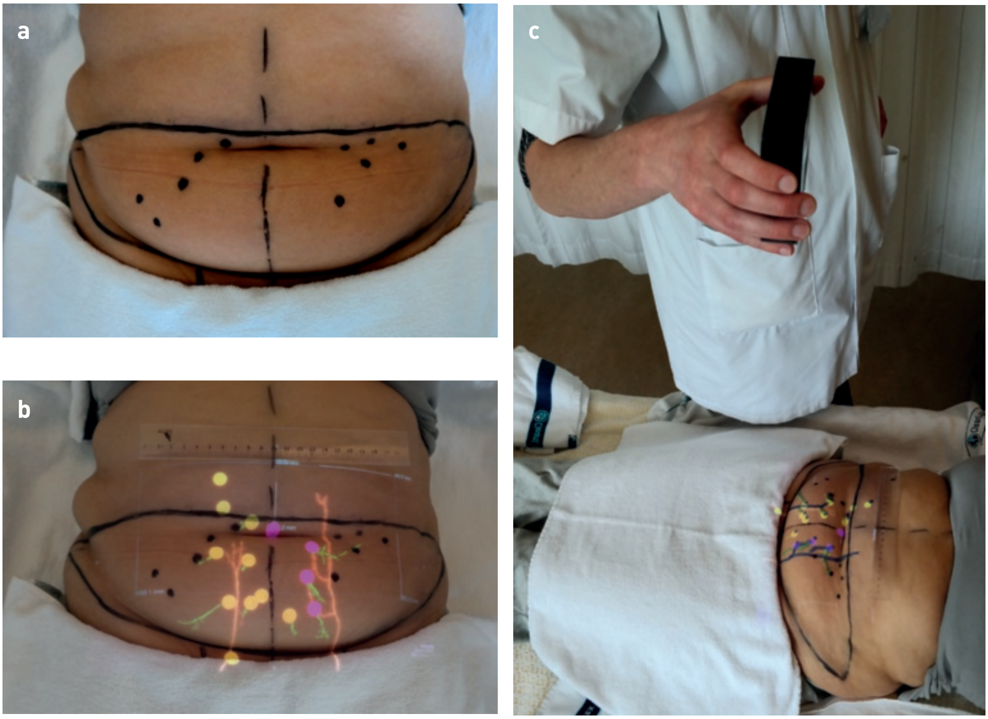



**Figure 2:** Handheld projection method. a) Black dots are determined following the standard Doppler protocol. b and c) The colored image is subsequently projected, showing the intramuscular (orange) and subcutaneous (green) branching pattern of the DIEA with its perforators (yellow and purple). A ruler is used to ensure an accurate scaling of the projected image.

## RESULTS

In these preliminary results, Doppler US, projection, and intraoperative data were available for nine patients. A total of 88 locations were marked with the use of Doppler US and a total of 100 perforators were projected ($p$ = 0.38). In these 100 projected perforator locations, a Doppler signal was audible at 98 locations.

In total, 34 perforators were transplanted and the total number of correctly identified perforators was 19 locations; 56.9% ± 31.4% using unidirectional Doppler US, whereas the projection method correctly revealed 29 locations; 84.3% ± 25.8% ($p$ = 0.030).

The average distance from the intraoperative perforator for Doppler US and the projection method was respectively 7 ± 4 and 4 ± 3 mm ($p$ = 0.009), although only the coordinates of the perforators within a 1-cm radius were reviewed.

## DISCUSSION

With unidirectional Doppler US alone, an arterial subcutaneous signal cannot be differentiated from a signal of the fascial penetration point. Projecting the intramuscular course of the deep inferior epigastric arteries and perforator locations onto the abdominal wall indicates the exact point of penetration of the perforator through the fascia. Not only would more information be available but also the time spent on preoperative planning might be lower with the projection technique. Performing the operations on the Vitrea fX Workstation takes only 15 minutes and the projection on the patient including confirming the locations with a unidirectional Doppler US probe takes around 2 minutes.

Obese patients may benefit from this technique; in this pilot study, two patients had a BMI >30 where the projection method showed the perforator locations more accurately than Doppler. A larger study cohort is necessary to investigate this.

The center of the umbilicus at the height of the fascia is not always obvious. Several transplanted perforators were submillimetric accompanied by a larger perforator, which were not specifically planned on CT but accounted for in the results. All transplanted major perforators were identified on CTA. Therefore, the previously mentioned 84.3% positive identification can be regarded an underestimated percentage.

The presented method is based on CTA images, whose quality should be sufficient for diagnostic purposes in order to produce a 3D reconstruction. Although in this study 3D reconstructions were created in Toshiba's VitreaAdvanced fX Workstation software, the 3D reconstruction method could be adapted to work with other 3D visualization software as well. A limitation in this study is that the projection method is operator dependent. The projector should remain perpendicular to the patient and centered at the umbilicus to avoid incorrect projections. During this process the operator of the projector inevitably introduces a tremor when holding the projector above the patient, which is disadvantageous for the accuracy. Other systems are capable of displaying anatomical data on the patient by using reflective markers and detectors, multiple cameras, or half-silvered mirrors. [14-18] However, this involves using an overcomplicated and bulky system, especially for the discussed procedure. We are therefore working on a simple minimalistic operating room compatible projection system with active feedback. This guarantees a steady, accurate projection onto the patient while remaining handheld and easy to use.

A minimalistic setup to reach preoperative augmented reality by projection on the abdomen is presented. However, the abdomen is not the only part of the body suitable for projection, as this method can be applied in other surgical fields as well for the visualization of important structures. These areas will be investigated on feasibility after the stabilized self-correcting handheld projection apparatus has been completed.

## CONCLUSION

A new method of displaying vascular mapping essential for DIEP flap reconstructions onto the patient's abdomen is presented in this paper. The projection method is not only capable of correctly identifying more perforators used for transplantation than unidirectional Doppler US but also more accurate in pointing out the corresponding perforator found intraoperatively. Additionally, the intramuscular course and subcutaneous branching of the deep inferior epigastric arteries can be visualized.

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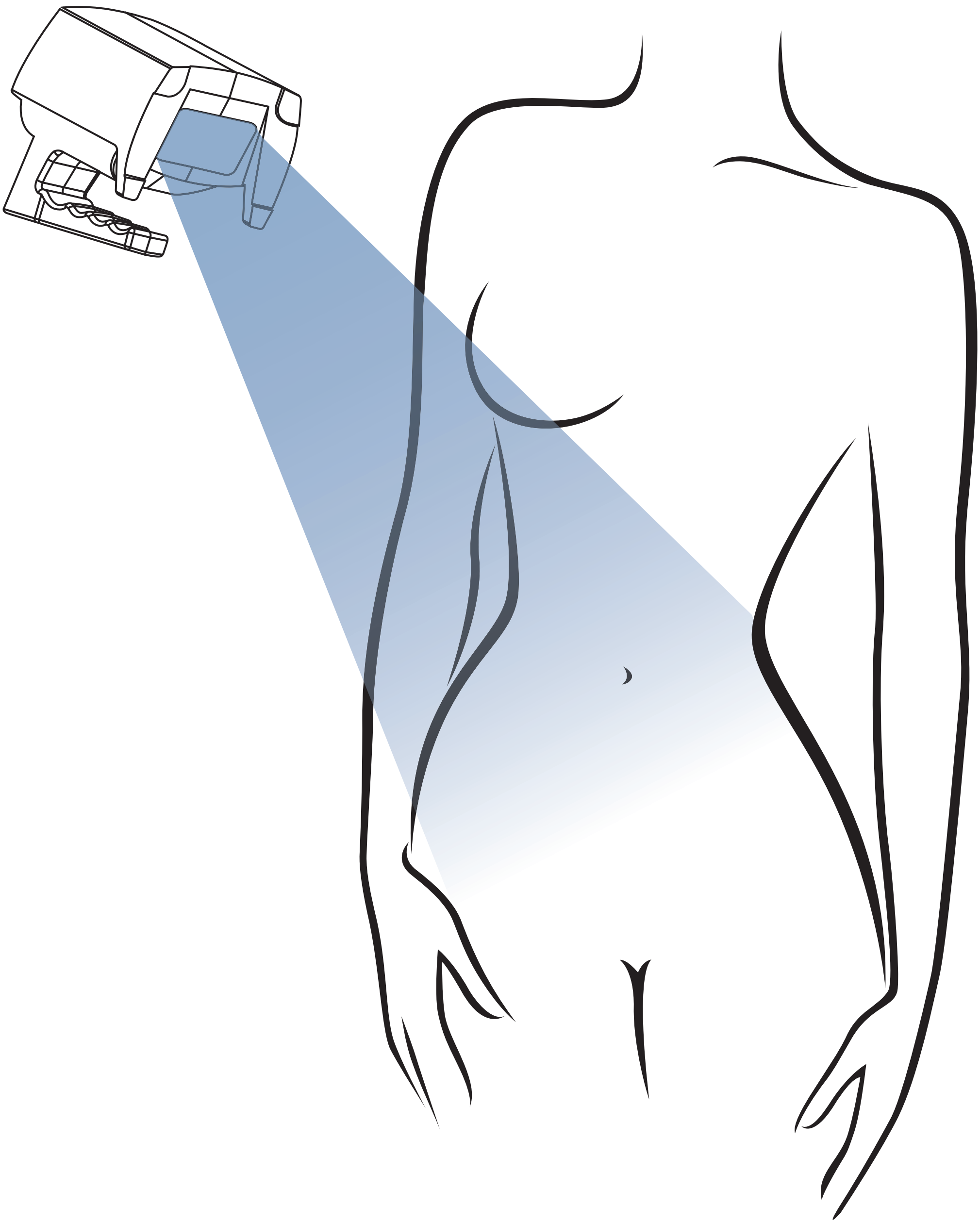
# CHAPTER 3

## The merits of decision modelling in the earliest stages of the IDEAL framework - an innovative case in bilateral breast reconstruction



## ABSTRACT

IDEAL framework aims at improving the evidence base of available surgical innovations. However, the development of such innovations and collection of evidence is costly. Surgical innovation can provide more value for money if innovations are evaluated in an early stage, where evaluations can inform the decision whether to stop or further develop an innovation. We illustrate how decision modelling can be readily adopted at the earliest stages (0-1) of the IDEAL framework, using an innovation in bilateral DIEP flap breast reconstruction as an example.

We quantified expected costs and quality-adjusted life years (QALYs) of the current treatment and compared this with an innovation aimed at reducing complications and surgery time. The maximum impact of eliminating all complications (headroom analysis) was explored. Second three scenarios with varying complication and surgery time reduction was modeled. Third, the maximum price of the innovation was estimated in a threshold analysis, based on its impact and societal willingness to pay.

The headroom analysis showed that when all complications associated with current treatment are prevented, up to €889 per patient is saved. Scenario analysis showed cost savings between €256 and €828 per patient. When surgery time is reduced by 15 minutes and complications by 50%, the innovation will remain cost-effective at €671 per patient.

In a field struggling with cost containment, decision modelling can help to separate promising innovations from costly failures in an early stage. In this example, decision modelling showed that it seems worthwhile to further develop the innovation.

## INTRODUCTION

Innovative medical technologies are being developed at a dazzling pace. Most technologies are aimed at improving patient health. As a result, we are healthier and live longer than ever.[1] However, only half of all new introduced treatments prove to be superior to the old treatment.[2] This implies that new is not always better. As evidence on the effectiveness of surgical innovations is often lacking or of poor quality, one can expect that surgical innovations used in clinical practice may not always improve health.[3] In reaction to this, the IDEAL framework was developed to provide a structural method of assessing a surgical innovation. IDEAL is an acronym for 'Idea, Development, Exploration, Assessment, Long-term study', representing the different phases in the assessment of a surgical innovation. The framework has been widely adopted and cited in over 300 publications.[4]

However, rigorous evaluation of surgical innovations is time-consuming and associated with high costs. Unfortunately, when reports finally become available on its efficiency and efficacy, the innovation is already in a advanced stage of development or implementation. To overcome this problem, one should reflect on the potential added value of the innovation prior to the costly development and research phases. After each IDEAL stage, one should carefully consider whether it is worthwhile to continue developing or researching the innovation.

Health Technology Assessment (HTA) can provide such insight of possible costs and benefits of surgical innovations. Decision modelling can help in mapping the current surgical procedure and its costs and benefits, as well as an ideal procedure without complications.[5, 6] A model can be created of the field where the innovation will be positioned, providing a mathematical framework which facilitates estimation of the consequences of health care decisions.[7] By progressively quantifying the current care pathway, e.g. mapping out all associated costs and consequences, insight can be gained in the total room for improvement ('headroom').[6] Although information regarding (cost-)effectiveness in an early development stage can be scarce, specific research methods are available to obtain informative results.[8]

Decision modelling determines the potential consequences of the innovation for clinicians, patients or society prior to development, so that the already limited funds can be redistributed to focus on the most promising applications or projects. It is increasingly acknowledged that when adopting surgical innovations, their advantages (e.g. health benefits) should outweigh their disadvantages (e.g. costs, risks).[9] This implies that innovations should only enter and proceed in the IDEAL framework if they have the potential to provide value for money. With the addition of decision modelling to the IDEAL framework, one has the opportunity to consider evidence in an early stage for each innovation. With healthcare costs ever increasing, such

information is not only desirable in terms of efficiency and efficacy, but mandatory in reducing development and research waste.
In this article, we illustrate the addition of decision modelling to the earliest stages of the IDEAL framework, in the case of a recent innovation in deep inferior epigastric perforator (DIEP) flap breast reconstruction surgery. A virtual surgical planning is created from Computed Tomography Angiography (CTA) and consists of suitable perforating blood vessel locations and their intramuscular trajectory, and additionally lymph nodes or flap volume delineations. [10-12] The planning is preoperatively projected onto the patient's lower abdomen and consecutively traced with a marker pen for intraoperative reference. By aiding the surgeon in displaying the locations of the most suitable perforators on the patient, it has the potential for faster surgery times as well as reducing complications and thus increase patient outcome.[13-16] With this illustration we aim to increase understanding and demonstrate the value and feasibility of decision modelling applicable to surgical innovations.

## METHODS

We started out with the creation of a decision model for the DIEP flap breast reconstruction procedure. Based on this decision model, three types of analyses can be performed to inform the decision whether or not to develop or study an innovation: headroom, scenario and threshold analyses. These three analyses and their application to the presented innovation are described below.

A headroom analysis compares the current situation with a perfect intervention. For example, if a surgical technique aims at reducing perioperative mortality, one can model the current perioperative mortality and associated costs, to calculate the maximum life years that could be gained through such an innovation. The lower the current perioperative mortality, the lower this upper bound will be, and the lower the potential value of the innovation.

In order to perform a headroom analysis, the current situation should be modelled first. In the case of DIEP flap procedure, current clinical workflow consists of a resident preoperatively assessing the abdominal vasculature, the DIEP flap breast reconstruction surgery, and several days of post-operative hospitalization (figure 1). The model was constructed in close consultation with experts. It comprises all procedure times and resources including possible repeated surgery after complications and alteration in quality of life. Currently, the primary DIEP flap surgery is performed within 8.5 hours on average by two surgeons and a resident, followed by a hospital stay of 5 days (Table 1). We modelled three types of possible complications from primary surgery: fat necrosis, abdominal morbidity (e.g. dehiscence, herniation) and (partial) flap loss. If these occur, surgery is repeated, performed by one surgeon and resident lasting only 1.5 hours to 2 hours. Hospital stay after repeated surgery was assumed to be 3 days. Based on literature, fat necrosis was found to occur in 10.9% of patients, while abdominal morbidity occurred in 5.7% and partial flap loss in 5%.[15, 17-19] The total costs were calculated in Euros by multiplying resource use (e.g. time) with unit costs (e.g. personnel costs). Effectiveness was determined through Quality-Adjusted Life Years (QALYs). This generic measure combines quality and length of life into a single index number, where 1 QALY equals a year in perfect health. QALYs for patients with and without complications were derived from published literature.[19] All parameters used in the model are based on published literature, expert opinion, and hospital records and can be reviewed in table 1.



For the headroom analysis, we investigated how much room there was for improvement by comparing a 'perfect' DIEP flap surgery without any discomfort or complications with the current situation. The maximum gain in the procedure (effectiveness gap) is obtained by subtracting the QALYs of the current situation from the perfect procedure. To monetarize this calculated headroom, the effectiveness gap was multiplied by the willingness to pay (WTP); representing the amount of money society is willing to pay for one QALY. We applied a WTP value of €36.500, based on the UK threshold which lies between £20.000 and £30.000. [20]

Second, scenario analyses can be performed by questioning 'what if'. For example, it can be calculated what the consequences are if perioperative mortality is reduced by 50%. These scenarios can be drafted in collaboration with stakeholders, using a simple or more advanced approach.[21, 22]

To examine the potential consequences of the DIEP flap innovation under a range of realistic circumstances three scenarios were drafted; conservative, realistic and optimistic.

We modelled the expected costs and QALYs for DIEP flap breast reconstruction with the innovation in each of these three scenarios, as well as the differences between these scenarios and the current situation. The scenarios were drafted in close consultation with surgeons and residents who have experience with DIEP flap surgery. For the conservative, realistic and optimistic scenario, the probability of complications was estimated to decrease by 5%, 10% and 25%, respectively, and surgery time by 15, 30 and 45 minutes compared to the current situation. Other parameters were equal to the current situation.

Third, threshold analysis can be performed to explore the threshold at which a specific outcome occurs.[22, 23] For example, this analysis can identify the maximum percentage of perioperative mortality that results in the innovation being cost-effective. Also, if the expected costs of the innovation are unknown, the analysis can identify at which maximum costs the innovation will remain cost-effective.

Given a specified reduction in complications and primary surgery time, we explored the maximum costs for the innovation to remain cost-effective. For the reduction in time for primary surgery, we used the values from the scenario analysis; 15 minutes, 30 minutes and 45 minutes. For complication reduction we explored a range between 0% and 50% of the complication incidences in current practice. The model was created and all analyses were performed using Excel (Office 2007, Microsoft, Redmond, USA).

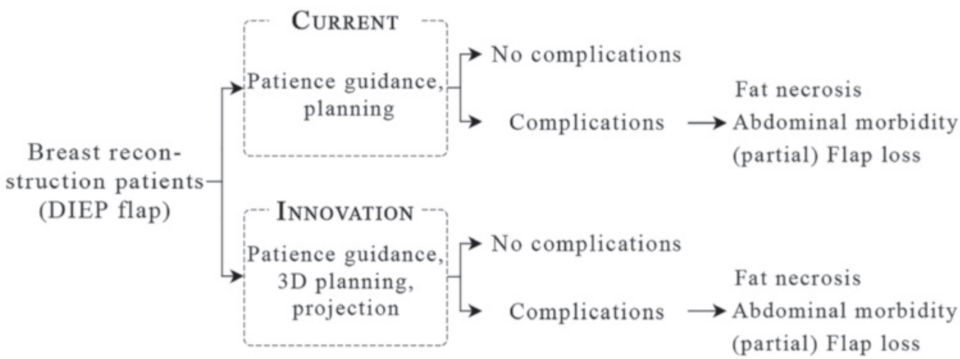



**Figure 1:** Simplified representation of the decision model, comparing the current strategy with the innovation

**Table 1:** Detailed overview of all model parameters for current practice. * Based on "Collective Bargaining Agreements"

| **Input Parameter** | **Value** | | **Source** |
|---|---|---|---|
| Costs (€) | | | |
| *Unit costs* | | | |
| CT-scan (euro/scan) | 275 | | Radboud university medical center |
| OR use (euro/hour) | 712 | | Radboud university medical center |
| Hospital stay (euro/day) | 478 | | L. Hakkaart-van Roijen [24] |
| *Personnel costs (euro/hour)* | | | |
| Surgeon | 79 | | L. Hakkaart-van Roijen [24] * |
| Resident | 33 | | L. Hakkaart-van Roijen [24] * |
| Resource use (time) | | | |
| *Time (current practice)* | | | |
| OR use for primary surgery (hours) | 8.5 | | Radboud university medical center |
| OR use for repeated surgery (hours) | | | |
| Fat necrosis | 1.5 | | Expert opinion |
| Abdominal morbidity | 2 | | Expert opinion |
| Partial flap loss | 1.5 | | Expert opinion |
| Hospital stay after primary surgery (days) | 5 | | Radboud university medical center |
| Hospital stay after repeated surgery (days) | 3 | | Expert opinion |
| *Work duration and personnel (minutes)* | | | |
| Patient guidance and preoperative planning | | | |
| 1 Resident | 45 | | Expert opinion |
| *Work duration (hours)(current practice)* | | | |
| Primary | | | |
| 2 Surgeons | 8.5 | | Radboud university medical center |
| 1 Residents | 8.5 | | Radboud university medical center |
| Repeated surgery | See OR use | | |
| 1 Surgeon | | | Expert opinion |
| 1 Resident | | | Expert opinion |
| Transition probabilities | | | |
| *Current practice (Computed tomography)* | | | |
| Fat necrosis after primary surgery | 0.109 | | Casey et al.[17] |
| Abdominal morbidity after primary surgery | 0.057 | | Gacto-Sanchez et al. [18] |
| Partial flap loss after primary surgery | 0.050 | | Teunis et al.[15] |
| **Quality-adjusted life years** | **Utility** | **QALYs** | **Source** |
| Without complications | 0.85 | 30.690 | Chatterjee et al.[19] |
| Fat necrosis | 0.77 | 30.645 | Chatterjee et al.[19] |
| Abdominal morbidity | 0.765 | 30.677 | Chatterjee et al.[19] |
| Partial flap loss | 0.77 | 30.645 | Chatterjee et al.[19] |

## RESULTS

We calculated that in the current situation a bilateral breast reconstruction with the DIEP flap method has an expected cost of €10.969, with a corresponding number of 30,68 QALYs per patient (Table 2).

Our model showed that in a perfect situation, surgery without complications, a result of 30,69 QALYs per patient could be achieved. The unrounded difference of 0,0079 QALYs represents the effectiveness gap. This implies that any innovation that eliminates all complications can yield on average a maximum of (0,0079 QALYs x 365 ≈) 3 days in perfect health per patient. In monetary terms, this amounts to (€36.500 x 0,0079 =) €289. In addition, eliminating all complications results in an average cost saving of €600 per patient. The headroom for a bilateral DIEP flap breast reconstruction is therefore €889 in total.

The three scenario analyses showed potentially cost saving results and only a minor improvement in QALYs (Table 2). If the DIEP flap innovation reduces 5% of all complications, and reduces surgery time with 15 minutes (conservative scenario), this results in cost savings of €256 per patient, while gaining 0,0004 QALYs. In the realistic scenario, on average €512 is saved, while gaining 0,0008 QALYs. Lastly, the optimistic scenario with a 25% complication reduction and 45 minutes decrease in surgery time resulted in cost savings of €828 with each procedure, with a QALY increase of 0,0020.

The threshold analyses show the acceptable costs of the proposed innovation, given a certain reduction in complications and surgery time (figure 2). If the DIEP flap innovation reduces surgery time by 15 minutes, without any impact on complication rates, the innovation is cost-effective if it costs up to €226 per surgical procedure. If in addition the DIEP flap innovation reduces complications by 50%, these maximum costs may rise up to €671. If the innovation both reduces 50% of complications and reduces surgery time with 45 minutes, it is cost-effective if it costs up to €1.122 per patient.

**Table 2:** Results of scenario analysis per patient in rounded Euros. Costs for repeated surgery are based on incidence rate and average cost for surgery if complications arise.

| Parameter | Standard care | Conservative | Realistic | Optimistic |
|---|---|---|---|---|
| Patient guidance | 25 | 25 | 25 | 25 |
| CT scan | 275 | 275 | 275 | 275 |
| Primary surgery | 7 679 | 7 453 | 7 227 | 7 001 |
| Repeated surgery | 291 | 276 | 261 | 218 |
| Hospital stay primary surgery | 2 390 | 2 390 | 2 390 | 2 390 |
| Hospital stay for complications | 310 | 294 | 279 | 232 |
| Total costs | 10 969 | 10 713 | 10 457 | 10 141 |
| **Cost savings** | - | 256 | 512 | 828 |
| **QALYs** | 30.6821 | 30.6825 | 30.6829 | 30.6841 |

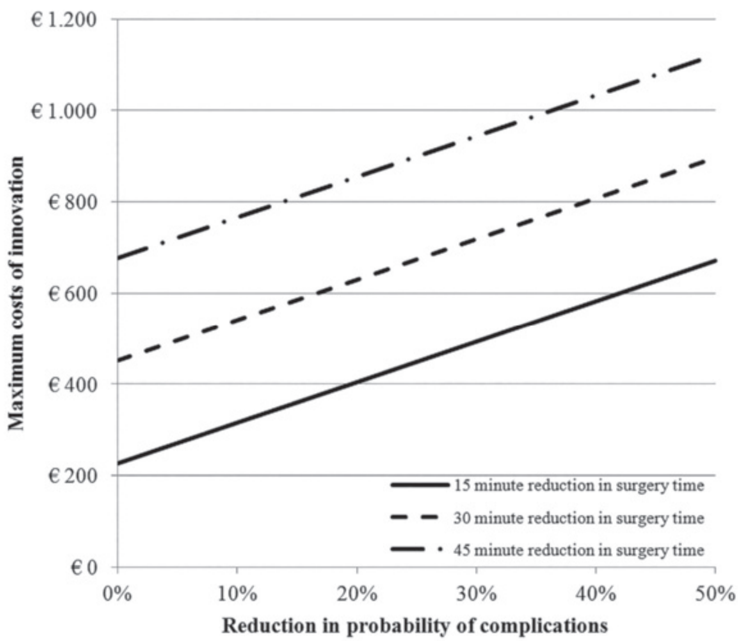



**Figure 2:** Acceptable costs for the innovation per patient at different surgery times and complication reduction rates.

## DISCUSSION

Our early decision model for DIEP flap breast reconstruction shows how such analyses provide valuable insight into the potential consequences of surgical innovations before development and/or clinical research. In the model we found that the intraoperative complication rate in the DIEP flap breast reconstruction rate is relatively small and therefore has relatively little impact on the quality of life. However, by reducing time spent on the primary surgery, as well as by reducing complications and the associated surgery, costs are reduced. Early decision modelling has not only the ability to investigate whether an innovation is potentially worthwhile, but also in which segment has the most potential. By running a new innovation through these analyses, one could decide whether it is worthwhile to further invest in the innovation prior to extensive development work, by comparing these costs with the innovation's cost-saving potential. Also, a preliminary price for the said innovation can be estimated to make the development worthwhile.

In a field of new technologies, not all expected advantages can be proven in advance with hard evidence. Estimations will have to be made, as no literature exists describing the consequences of the innovation in daily practice. The model is based on the most reliable data available at the time, such as expert opinions or the usage of the innovation in neighbouring fields, and will inherently contain errors. Conclusions regarding cost-effectiveness therefore should be used as a preliminary insight into how the innovation will keep up on an estimated cost-effective basis and can help in the decision to pursue the innovation or divert funding. To keep the illustration simple and show how the analyses can guide decisions regarding development or research of innovations, we decided to present only point estimates, representing the average expected outcomes for a typical patient population. In reality, there is uncertainty surrounding these outcomes, because of the uncertainty in for example complication rates. Uncertainty surrounding the input parameters for the current DIEP flap breast reconstruction can easily be addressed by assigning distributions and using simulation methods, as is standard practice in decision modelling in health care.[22] This will allow for the calculation of confidence intervals surrounding the room for improvement and other outcomes.

When performing an early modelling study it is important to choose relevant outcomes for the field in which the innovation will be positioned. In this paper, we mainly focused on the costs and QALYs for bilateral DIEP flap breast reconstructive surgery. QALYs have the advantage of converting utility value to monetary value, and addressing the impact of positive (and/or negative) events. The assessed events should have valid consequences for the patient, clinician or society. Using early decision modelling may provide clinicians, developers, and policymakers with new insights concerning the consequences and viability of their innovation, particularly pertaining to value for money. In a field struggling with cost containment, such information can prove key to separating promising innovations from costly failures.[9] Prior to investments in development or research, the care pathway should be analyzed for sufficient room for improvement. Based on carefully selected outcomes, plans may be adjusted or scrapped, eventually reducing research waste on economically unviable innovations in practice.

Where the IDEAL framework is valuable for assessing new ideas in practice, the step of evaluating whether an innovation is potentially economically viable is lacking, and should be considered a valuable addition. This also fits perfectly into the recently proposed extended IDEAL framework for devices (IDEAL-D)[25] Previously, products have been developed with limited or no added value due to insufficient assessments and guidelines, and efforts are made to 'disinvest' in procedures with limited or no added value.[26, 27] To have not invested in technologies of limited value in the first place by means of decision modelling seems a much better alternative. Even the most basic analyses can already provide insight, especially if there is little headroom available. With the ability to determine various parameters during a procedure, innovations could be steered towards more cost-effective solutions. Of course, one could question when the results of such an early analysis are sufficiently high to warrant further development and research. In absence of a budget constraint, any innovation where the headroom exceeds its market price has potential value and should be developed. If the budget is constrained, a portfolio of innovations could be assessed to select those with the highest potential value for money. In the case of the DIEP flap breast reconstruction, the most gain could be found in terms of reducing costs, instead of improving quality of life. Since there is no explicit budget constraint, and the headroom exceeds the expected development and production costs of the technology, it seems worthwhile to evaluate the actual costs and effects in clinical practice. Therefore, the IDEAL framework will be followed in the upcoming development steps. A randomized controlled trial is planned in the near future, in which 78 patients will be included. By recording intra- and postoperative complications, surgery and planning times as well as surgeon workload we will be able to determine the clinical, short-term, patient-centered and feasibility outcomes as advised by the framework to continue improving breast reconstruction surgery without making unsubstantiated financial decisions.

## CONCLUSION

The IDEAL framework provides detailed information about developing and researching surgical innovation as safety and efficacy are concerned, but lacks an initial crucial step of investigating whether an innovation could recoup the investment made in its planned clinical setting. We have demonstrated that the incorporation of decision modelling into the IDEAL framework, as applied to the case of bilateral DIEP flap breast reconstruction surgery, can be useful. Our example shows that early HTA should be considered in the earliest phases when following the IDEAL framework for surgical innovations, and further development of the innovation will be worthwhile.

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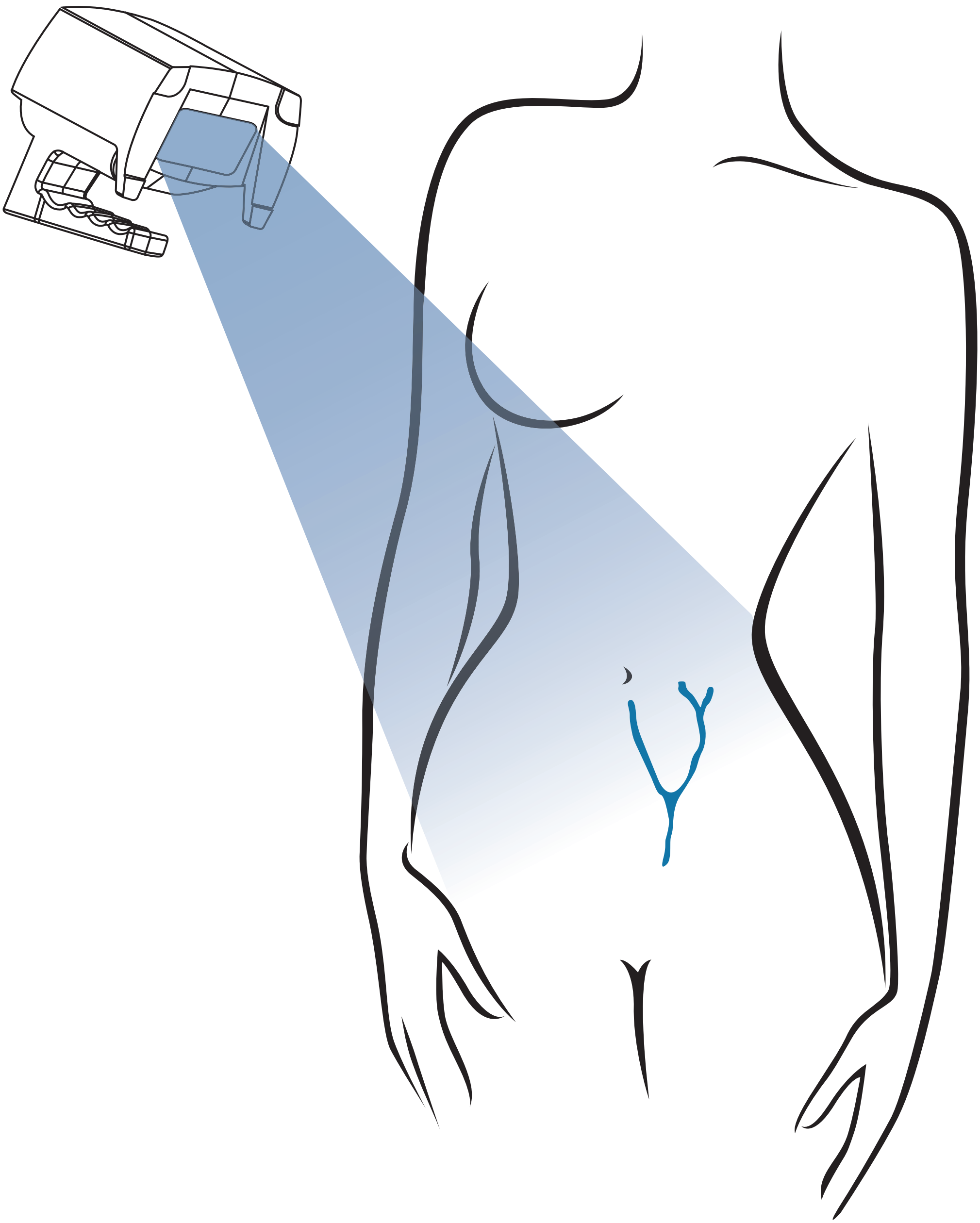
# CHAPTER 4

## The benefits of using innovative imaging techniques: A randomized controlled trial in breast reconstructive surgery



## ABSTRACT

**Background:** In Deep Inferior Epigastric Artery Perforator (DIEP) flap breast reconstructions, a free tissue flap from the abdomen is shaped into a breast and transferred to the thorax. Survival of this free flap relies on miniscule blood vessels, so-called perforators, providing blood supply to this newly moulded breast. Preoperative mapping of these randomly distributed blood vessels is of the essence to avoid complications.

**Objective:** To investigate whether the pre-operative projection of a virtual 3D planning based on computed tomography angiography onto the abdomen leads to more correctly identified perforator locations and less operation time spent on dissecting the free flap compared to the commonly used Doppler ultrasound planning method.

**Design, setting and participants:** Randomized, open, single-center, superiority trial in patients undergoing a DIEP flap breast reconstruction between December 2015 to March 2017 with 1 week follow-up. Randomized participants were 60 adults (projection n=33 [age 52 ± 9 yrs; BMI 26.5 ± 2.0], Doppler n=27, [age 50 ± 8 yrs; BMI 26.8 ± 2.7]) undergoing a DIEP flap breast reconstruction without lymph node transfer.

**Intervention:** Projection of a virtual 3D planning consisting of relevant vascular anatomy versus handheld Doppler ultrasound in order to predict perforating blood vessels locations.

**Main outcome measures:** Accuracy in detecting perforator locations; time spent on harvesting the free tissue DIEP flap; complications.

**Results:** Sixty patients provided 69 DIEP flaps for analysis. The projection method is capable preoperatively of displaying significantly more perforators compared to the Doppler method (61.7% ± 7.3% versus 41.2 ± 8.2%, respectively) (p=0.020)). During the procedure, flap harvest time is decreased by 19 minutes (136 ± 7 versus 155 ± 7 minutes, p=0.012). Complications were comparable across both groups.

**Conclusion:** Not only can more perforators be identified intraoperatively using the projection method compared to Doppler US, but there is also a significant time reduction in harvesting the DIEP flap.



**Trial registration:** Dutch Trial Register (NTR); identifier NTR5962.

**Funding:** None

## INTRODUCTION

Over the last decades the number and quality of imaging modalities has improved greatly, with many available for specified procedures. Various imaging techniques benefit the surgical area by affording knowledge prior the procedure. Basically, the indication for any imaging modality aspires the procedure to be performed easier, faster and with increased safety and thus improved patient outcome. The added value of preoperatively depicted anatomy is strongly dependent on comprehensibility of the images. In order to reach their full potential, post-processing of these images is highly recommended.



A case in hand for post-processing images is the well-established technique for autologous breast reconstruction, the deep inferior epigastric perforator (DIEP) flap procedure. This technique is performed after or during mastectomy. [1-4] Without breast reconstruction, surveys targeting breast cancer survivors reported that the patient's self-image of the body is decreased, experiencing feelings of sexual embarrassment, lowered self-esteem and increased anxiety.[5, 6] Through breast reconstruction, the psychosocial aspect and quality of life is increased.

By transferring the patient's own abdominal adipose tissue and skin to the thorax, one can mould this tissue into a natural looking breast. Also, in cases of post-operative lymphedema of the arm after axillary dissection, several vascularized lymph nodes from the inguinal region can be included in the free abdominal skin flap and transferred to the affected axilla. The minimal donor site morbidity and improved abdominal contour makes this the preferred method for many patients. [7] Furthermore, studies with long-term follow-up report satisfying esthetical results. [8, 9]

In this patient group, preoperative perforator mapping is of the essence. The vascular anatomy of the deep inferior epigastric artery and its perforators vary greatly between patients, and even within patients.[10] The survival of a DIEP flap relies solely on perforators providing adequate blood supply to the transferred tissue. In literature, various methods have been described to detect these randomly distributed perforators, such as colour duplex, fluorescent angiography, dynamic infrared thermography imaging, or magnetic resonance angiography. [11-17] However, bi-directional handheld Doppler ultrasound and computed tomography angiography (CTA) have remained the most popular modalities for DIEP flap perforator mapping. [18]

Computed tomography angiography is the gold-standard for pre-operative perforator mapping, but these images need to be post-processed further to reach their full potential. Through segmentation techniques performed on a workstation, a virtual DIEP flap planning consisting of perforator locations and intramuscular blood vessel trajectory can be created as a three-dimensional (3D) model. Furthermore, structures such as lymph nodes for treatment of lymphedema can be included, and total flap volume can be incorporated to aid in determining symmetrical breast volumes. As is the case with any imaging modality, the visualization of the anatomical structures remain only visible on a computer monitor.

To overcome the problem of having this advanced planning only available on a computer monitor, a self-aligning projection device was developed which is capable of displaying the virtual planning onto the patients lower abdomen at the equivalent anatomical position.[19-21] With the use of this innovative system, the operating surgeon has available the patient-specific vascular anatomy at the exact corresponding position on the abdominal wall. With such elaborated anatomical information at hand, surgery times, surgical accuracy and increased patient safety in relation to flap viability may be improved.

In the current randomized controlled trial we aimed to investigate whether projecting a patient-specific virtual DIEP flap planning onto the abdomen prior to surgery leads to easier, faster and improved patient outcome. It was hypothesized that the ratio of correctly identified perforator locations is increased and operation time spent on dissecting the free skin flap is decreased compared to the commonly used bi-directional handheld Doppler ultrasound method.

## DESIGN, SETTING AND PARTICIPANTS

This open single-centre randomized controlled superiority trial was conducted at the department of Plastic Surgery in the Radboud University Medical Center (Nijmegen, the Netherlands) from December 2015 to March 2017. Approval from the local medical ethical committee was obtained and the trial was registered in the Dutch Trial Register under identification number NTR5962. Informed consent was obtained from all participants and conducted in accordance with the Declaration of Helsinki. There were no conflicts of interest.

In order to be eligible to participate in this study, participants had to be 18 years or older; scheduled for direct, delayed, unilateral or bilateral deep inferior epigastric perforator flap breast reconstruction surgery and able to provide written informed consent. Exclusion criteria for this study were patients with intolerance or hypersensitivity to contrast agent Iomeron© (iomeprol); inadequate kidney function (due to contrast agent), or patients who would undergo a deep inferior epigastric perforator flap with an additional lymph node transfer.

Based on pilot trial data, the number of correctly preoperatively identified perforators found intraoperatively (true positives) in each flap could be estimated at a mean success proportion of 0.2 and standard deviation of 0.3. However, each flap is not entirely independent in double-sided breast reconstructions. The proportion of unilateral/bilateral breast reconstructions is respectively 0.615 and 0.385 based on retrospective data. For our superiority trial design, a double-sided $\alpha$ of 5% ($\alpha = 0.05$) with a power of 80% ($\beta = 0.20$) requires the inclusion of 34 women per group. To compensate for loss to follow up or missing data, a total of 38 patients per group was chosen, totalling the patients at 76. The estimated 60 minutes ±15 minutes (SD = 7.5 min) flap dissection time is hypothesized to decrease by 10 minutes in the projection group. Given an $\alpha$ of 5% ($\alpha = 0.05$, two-sided) and 38 independent observations per group, the power is calculated to 99.9%. However, in the last months of recruitment, the number of eligible participants decreased drastically as most of the upcoming patients underwent a lymph node transfer alongside the DIEP flap breast reconstruction (exclusion criterion). In consultation with the medical ethics committee and statisticians, the number of already included patients (n=60) was found sufficient to draw conclusions as a non-inferiority trial. Over the entire duration of the study no interim analyses were performed.



Stratification lists were randomly created in blocks of six for both single or double sided reconstruction and plastic surgeon. Upon inclusion, the patient (unilateral or bilateral) was allocated to a group (allocation ratio 1:1) corresponding to the list generated for the designated operating surgeon.

All patients were scanned with a Toshiba Medical Systems Aquilion One 320 slice CT scanner (Toshiba Medical Systems, Tokyo, Japan). Patients were injected with 80 ml Iomerion 300mg/ml (Bracco Imaging S.p.A., Milan, Italy), followed by bolus tracking at aorta bifurcation and a 8 second delay. Scans were acquired in caudal-cranial direction, ranging from trochantor minor to 8 cm above the umbilicus, and reconstructed with 1 mm slice thickness.

In the control Doppler group, a bi-directional handheld Doppler device (Dopplex SD2, Huntleigh Healthcare Ltd, Cardiff, Wales, United Kingdom) was used for perforator assessment. The Doppler device was held perpendicular to the abdominal skin and moved transversely, starting at the height of the umbilicus and moving caudally towards the os pubis, systematically covering the entire flap area. All sounds representative of perforators were indicated on the abdominal skin with a marker pen. These marked locations were measured from the umbilicus in a horizontal and vertical fashion to obtain coordinates and annotated on a case report form. For the patients in the projection group, a virtual 3D planning consisting of the vascular anatomy was created using a VitreaAdvanced fX Workstation (Vital Images, Toshiba Medical Systems Group Company, Minnetonka, USA). Within this virtual 3D planning, the deep inferior epigastric artery and its branching pattern was indicated, along with its significant perforators (diameter > 1 mm). The intramuscular trajectory was highlighted to aid in pre- and intraoperative perforator selection. In order to transfer the virtual planning to the patient, four stickers with patterns recognizable for the projection device were temporarily placed on the patients' anatomical landmarks: the umbilicus, symphysis, and bilateral anterior-superior iliac spines. The projection device was held in one hand above the patient, and it automatically aligned and projected the virtual planning onto the patient's lower abdomen (figure 2). All projected information was traced with a marker pen and the perforator locations measured using the same method as in the Doppler group (figure 3 and 4).

Four microsurgeons performing the DIEP flap surgeries were asked to collect data during and after the procedure. All flaps were harvested in two teams as per standard clinical operation technique; the DIEP flaps were elevated in a lateral to medial fashion, careful to preserve perforators. Prior to incision of the rectus sheath all locations of the intraoperatively found perforators were measured with the umbilicus as centre point, equal to the preoperative data collection method (figure 5). Next to the pre- and intraoperative perforator locations, the patient's demographics, pre-operative time, intra-operative complications and post-operative complications (follow-up), and harvest time per flap were recorded.

Data was analyzed as per protocol using the Generalized Least Squares (GLS) statistical technique in order to correct for the dependency between residuals from women with bilateral breast reconstructions. As covariates condition, surgeon and uni- or bilateral flap harvest was used. Furthermore, a Student's T-test was performed to assess the statistical difference between the ratio of intraoperatively found perforators and preoperatively located perforators in each flap.

All statistic analyses were performed using SPSS Statistics version 22 (IBM Inc., Chicago, United States of America), and all parameters were considered significant at $p \leq 0.05$.

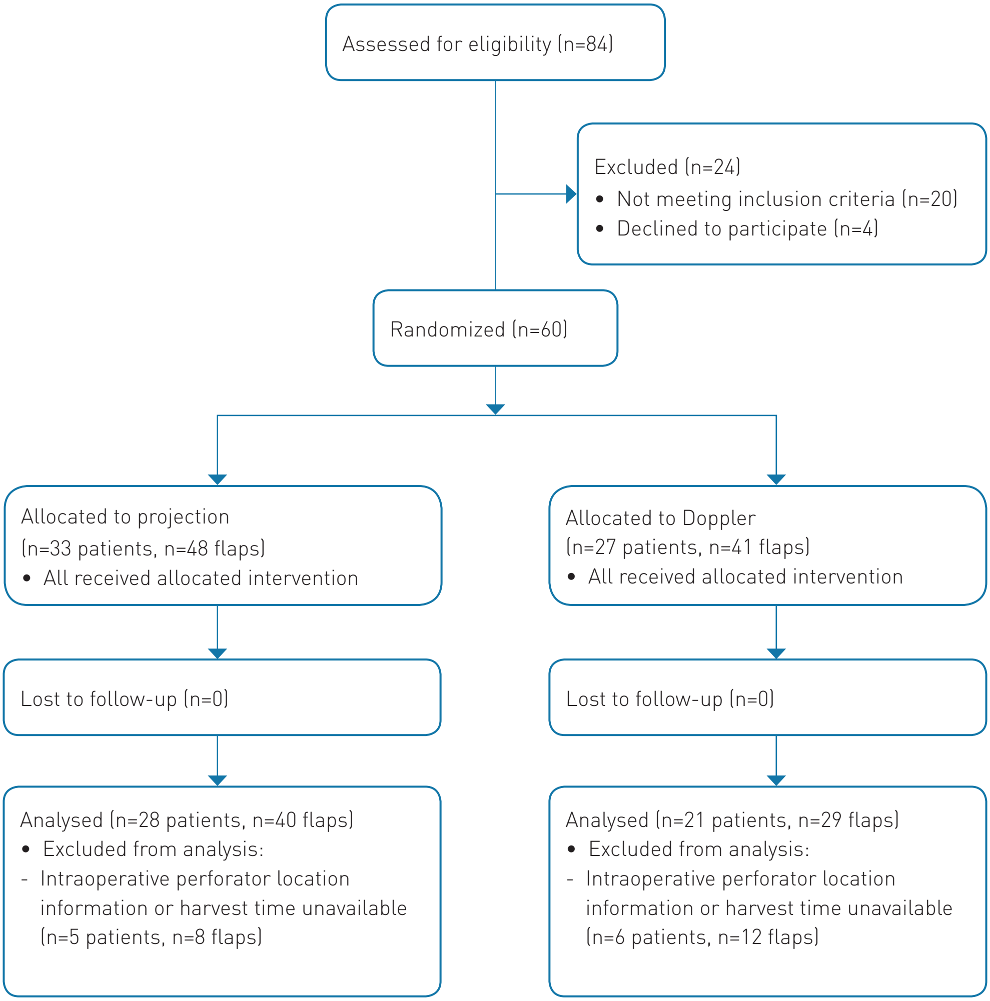



**Figure 1:** CONSORT flow diagram indicating the enrolment, intervention and analysis of patients.

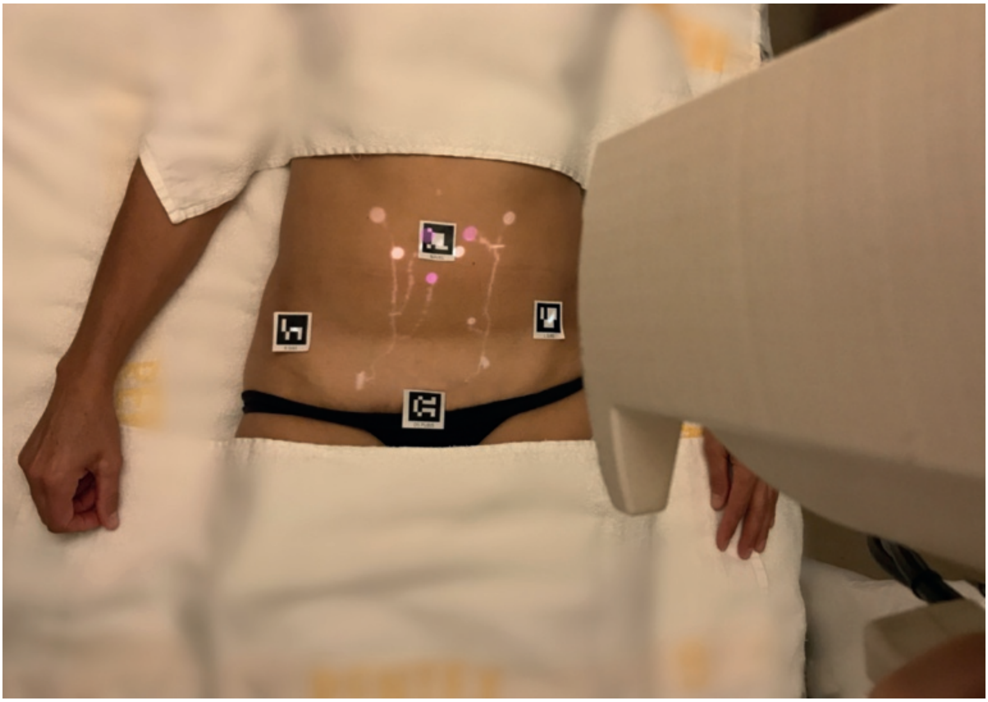


**Figure 2:** Virtual DIEP flap planning is projected onto the patient's abdomen. Black and white stickers are temporarily placed on anatomical landmarks. The yellow and pink circles indicate perforator locations, of which the pink were determined the most favorable. The yellow horizontal lines indicate the start of intramuscular trajectory from the deep inferior epigastric arteries, which are depicted as vertical orange lines.

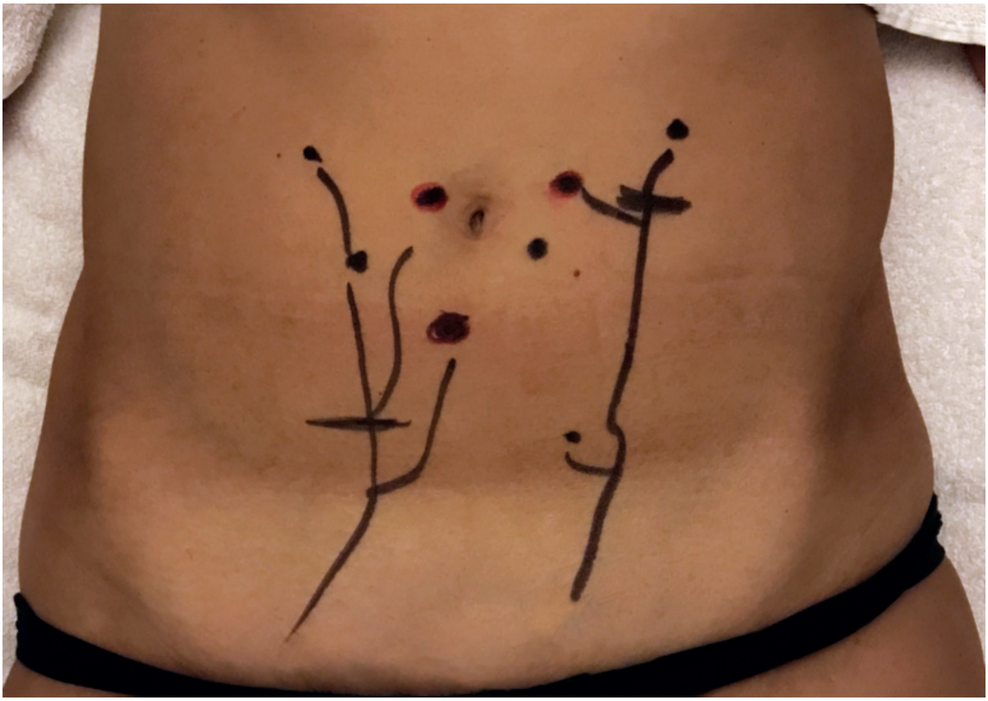


**Figure 3:** Status after tracing the projected image with a marker pen. The stickers are removed. The purple circles are extra highlighted. The horizontal lines indicate the start of the intramuscular trajectory.

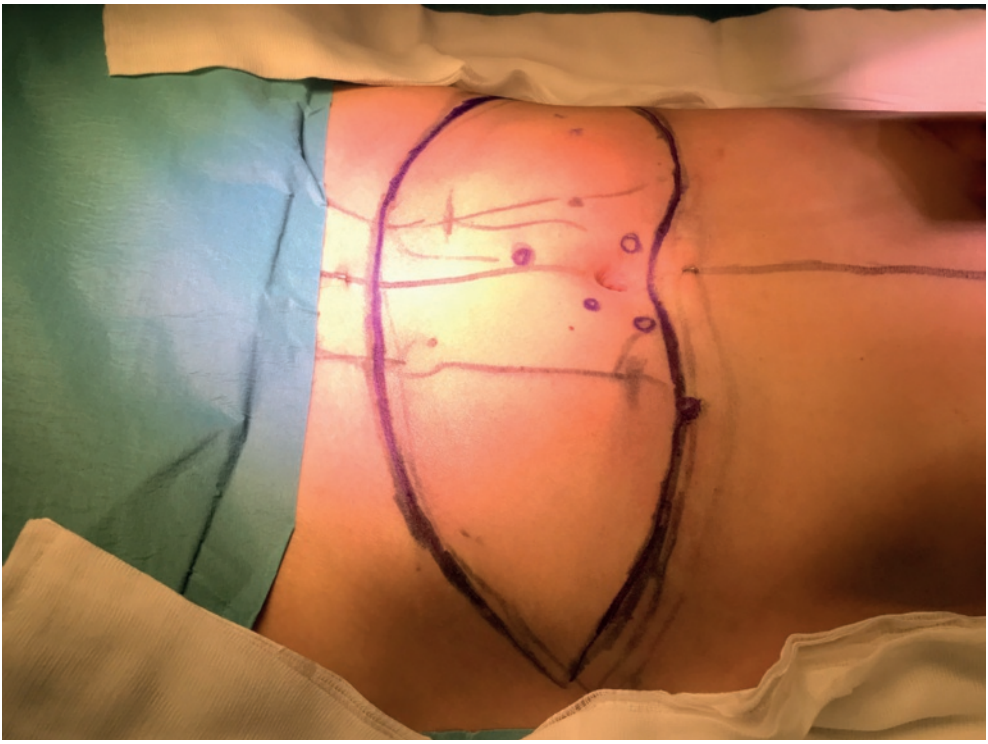


**Figure 4:** Delineation of the DIEP flap with perforator locations and vascular trajectory. Although the amount of abdominal adipose tissue is limited, it is sufficient for her planned unilateral breast reconstruction.

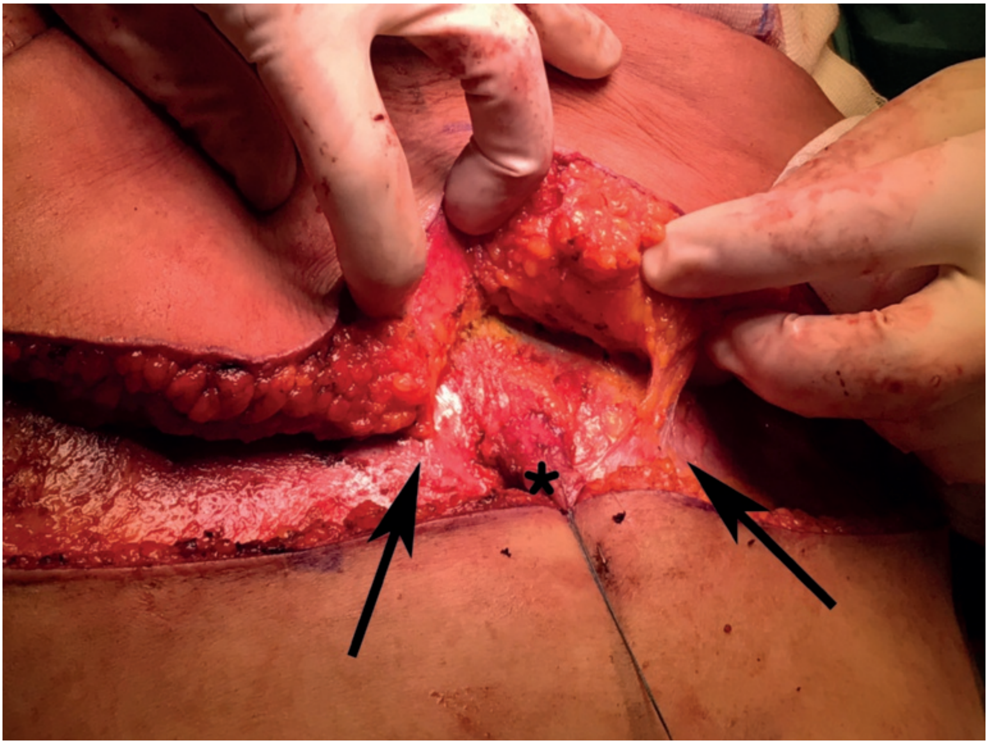


**Figure 5:** Intraoperative photo (top: caudal; bottom: cranial) during flap harvest. The umbilicus is illustrated with an asterisk. The most favorable perforators, as displayed through the projection method, are located at their predicted location (black arrows).

# RESULTS

In total 84 patients were screened for eligibility to participate in this study. Of the originally calculated 76 patients, a total of 60 patients were included in this randomized controlled trial and were assigned to either Doppler group (n=33) or projection group (n=27). These patients provided a total of 89 flaps of which 69 flaps could be analyzed, as pre- or intraoperative recorded parameters were not available for all flaps (figure 1).

The main study outcomes included the number of correctly identified perforators compared to intraoperative results in each harvested flap as well as the time required to harvest each flap. During the preoperative procedure the time spent to obtain a full perforator mapping took 20.0 ± 5.5 minutes in the Doppler group, whereas the duration of the projection method was 2.3 ± 0.8 minutes. This 17.7 minutes difference is statistically significant with p<0.001. In the Doppler group it was recorded that 41.2 ± 8.2% of all perforators were correctly identified intraoperatively. For the projection group this number calculated to 61.7% ± 7.3%; a significant difference of p=0.020.

Total time spent on harvesting a flap was on average 155 ± 7 minutes in the Doppler group, whereas the projection group showed 136 ± 7 minutes. This intraoperative time reduction of 19 minutes is statistically significant (p=0.012).

**Table 1:** Patient characteristics, pre, intraoperative and post-operative information for the control (Doppler method) and intervention (projection method) group. The p-value for the parameters are indicated, or were found to be not significant (ns).

| **Parameter** | **Doppler method** | **Projection method** | ***p*** |
|---|---|---|---|
| Number of patients | 27 | 33 | ns |
| Unilateral | 13 | 18 | ns |
| Bilateral | 14 | 15 | ns |
| Total number of flaps | 41 | 48 | ns |
| Age | 50 ± 8 yrs | 52 ± 9 yrs | ns |
| BMI | 26.8 ± 2.7 | 26.5 ± 2.0 | ns |
| Preoperative perforator localization time | 20.0 ± 5.5 minutes | 2.3 ± 0.8 minutes | 0.000 |
| Perforator localization accuracy | 41.2 ± 8.2% | 61.7% ± 7.3% | 0.020 |
| Duration of flap harvest | 155 ± 7 minutes | 136 ± 7 minutes | 0.012 |
| Complications | | | |
| During flap harvest | 0 | 0 | ns |
| Flap revisions | 2 | 3 | ns |
| Flap loss (after revision) | 1 | 2 | ns |
| Infection | 1 | 2 | ns |
| Abdominal dehiscence | 7 | 6 | ns |

The post-operative complications recorded in this study were infection, dehiscence and flap loss and part of the standard risk of the procedure. A total of three flaps were lost despite revision surgery of the reconstructed breast as the recipient vessels were inadequate in diameter or fragile as result of radio- and chemotherapy. All complications were not significant between both Doppler and projection group. These results can be reviewed in table 1.

## DISCUSSION



In this study it was explored whether the presented projection method is a feasible alternative to handheld Doppler. Although handheld Doppler easily accessible, the downside is its limited penetration depth in more obese patients, the inability to distinguish between superficial arteries and perforators, lack of information regarding the epigastric arteries and the large interobserver variability. Klasson et al. published a study questioning the added value of CTA as preoperative imaging, however we have shown that when CTA is post-processed to full extent it contains valuable information essential to a DIEP flap breast reconstruction.[22]

By creating the presented virtual DIEP flap planning in this study more anatomical information can be obtained compared to handheld Doppler alone. This virtual 3D planning is created on a post-processing workstation by an experienced technical physician in approximately 10 minutes, however, this work can be done by any healthcare professional when following a post-processing protocol for obtaining the information required for the projection. Tracing of the data onto the patient along with features such as flap volume, intramuscular trajectory and lymph node locations by means of projection takes only two to three minutes. There remains a significant time advantage when using the projection method compared to Doppler ultrasound: physical examination time is decreased, not only decreasing patient discomfort but also decreasing the surgeon's pre-operative workload. Finally, with a mean decrease of 19 minutes in operating time, the procedure is performed more efficiently with all the associated benefits.

For both the Doppler and projection groups, there were patients in whom intra-operative measurement were difficult to perform as the centre of the umbilicus was not always apparent. To overcome this systematic error, a radius of 1 cm around each measured perforator was taken during analysis. In three cases in the Doppler group and five in the projection group the measurements evidently showed a systematic shift between the preoperatively and intraoperatively captured data of more than one centimetre, for which the data was transposed to fit the most data points.

The data was gathered from one single health care centre. The originally designed superiority trial was not conducted in full as many DIEP flaps were extended with inguinal lymph nodes after positive clinical post-operative results for lymphedema patients. The included patients were able to provide sufficient data to convert to an overpowered non-inferiority trial. Future studies will be set-up in a multi centre fashion to include a larger number of patients, investigate different end-users and their experience with the new projection technique.

Besides perforator mapping through CTA, magnetic resonance angiography (MRA) can provide similar images without the necessity of ionizing radiation. Furthermore, recent literature described a method to visualize the epigastric artery as well as its perforating vessels without injected intravenous contrast agents.[23] The post-processing workstation used in this randomized controlled study is capable of processing images acquired through MRA, hence, the virtual 3D planning can be derived from this imaging modality. Future studies will focus on exploring the possibilities of creating a virtual 3D planning based on this non-contrast-enhanced MRA imaging modality.

A further optimization of unilateral breast reconstruction could be the addition of 3D-stereophotogrammetry to this procedure to identify the unaffected breast volume.[24, 25] Combining this preoperative information with CTA, capable of depicting blood vessels and the amount of abdominal fat, it is possible to preoperatively plan the shape and volume of the flap. By creating and projecting this virtual 3D flap planning, one might achieve a 'one-step unilateral breast reconstruction', in which the contralateral breast is lifted and reduced to match the preoperatively planned reconstructed breast in volume and shape, including an intraoperative nipple reconstruction.

Within breast reconstructions, we are currently investigating the projection of perforator locations, intramuscular trajectory and volume calculations in profunda artery perforator (PAP) flap breast reconstructions. As the technique presented in this paper has the potential for wider application, other applications outside the breast reconstructive area are also being explored, such as sentinal lymph node localization, displaying lymphatic vessels in lymphovenous shunt procedures, and patient or student education.

## CONCLUSION

The projection method is capable of preoperatively displaying significantly more perforators in less time compared to Doppler method. During the procedure, flap harvest time is significantly decreased.

Not only can more perforators be identified intraoperatively using the projection method; but there is also a significant time reduction in both the pre- and intra-operative setting.
DIEP flap breast reconstruction patients as well as health care professionals can benefit from planning and projecting the DIEP flap and it's anatomy onto the patients abdominal skin prior to surgery. Additional applications are being explored outside the breast reconstructive procedure.

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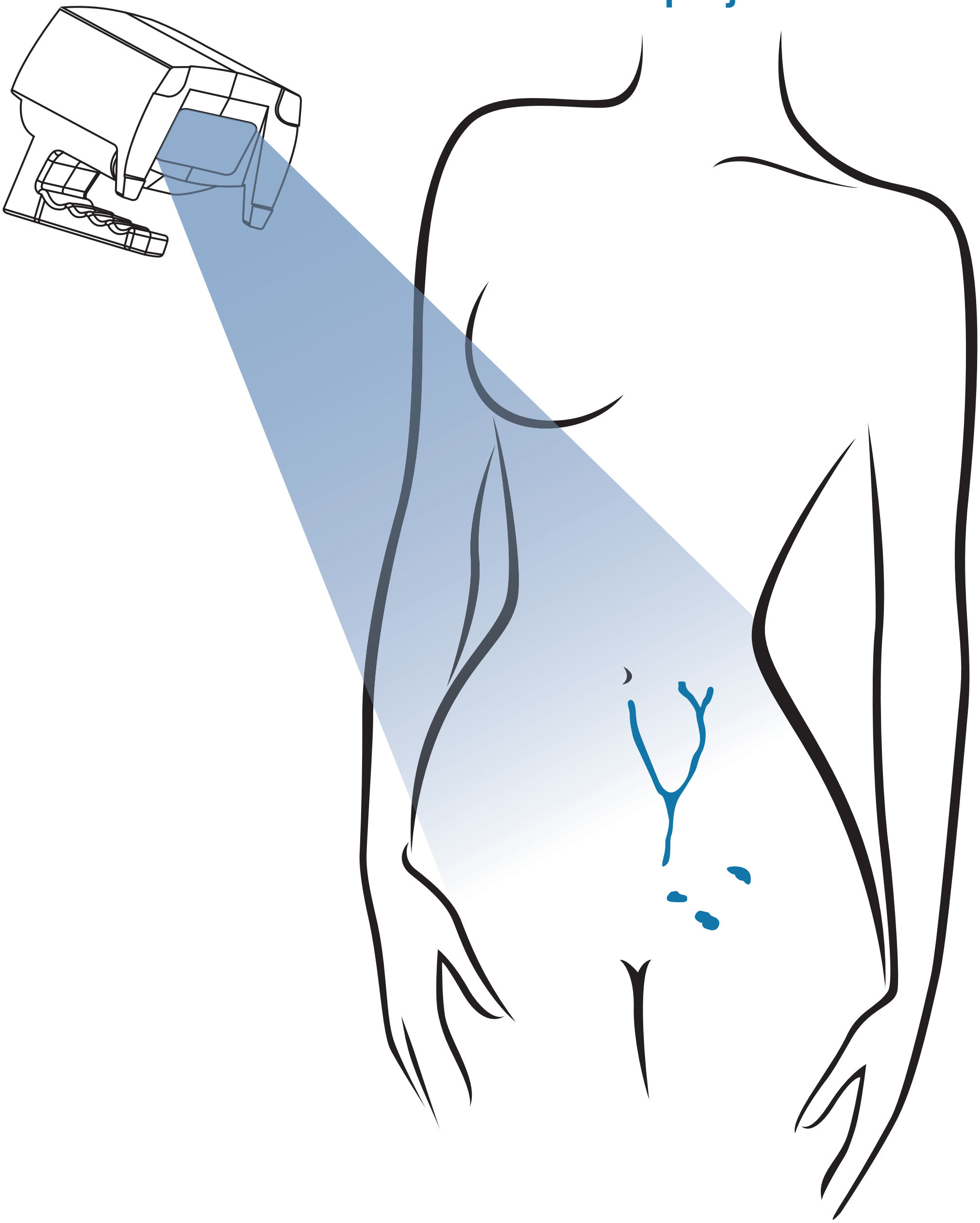
# CHAPTER 5

## Displaying inguinal lymph nodes prior to transplantation in a deep inferior epigastric perforator flap breast reconstruction using an innovative projection method



## ABSTRACT

Lymphedema of the arm is a common postoperative complication as a result of breast cancer surgery. One of the surgical treatments comprises modification of a deep inferior epigastric perforator (DIEP) flap breast reconstruction to facilitate additional lymph node transplantation from the inguinal area. Using computed tomography angiography (CTA), the distribution of these lymph nodes can be assessed. A virtual planning based on this CTA created for the DIEP flap is presented, with the inguinal lymph nodes included, followed by preoperatively projecting this information on the patient's abdomen.

A total of 10 patients underwent the standard imaging protocol: A preoperative CTA to assess the vascular anatomy of the lower abdomen. A three-dimensional (3D) model of the blood vessels was produced, and the inguinal lymph nodes in this reconstruction were included. Preoperative projection of the 3D model onto the patients' abdomen and inguinal area was performed, followed by tracing of this image. Intraoperatively found lymph nodes were identified by touch and compared with the markings on the skin.

In all 10 patients, all lymph nodes located preoperatively were found intraoperatively within a 1-cm radius of the marking on the skin; and these were more easily located by two operating surgeons.

Virtual planning of lymph node transplantations in a deep inferior epigastric artery perforator flap breast reconstruction seems feasible and can be performed quickly. This additional visual support aids the surgeon in locating the lymph nodes in the inguinal area.

## INTRODUCTION

Lymphedema of the arm is one of the most common postoperative complications after breast cancer surgery, with an incidence ranging between 9% and 41%.[1-3] This impairing complication remains a challenge with few curative treatment options available. Single or a combination of therapies have been proposed in the literature and include various compression, physiotherapeutic, and surgical treatments.[1, 4]

One of the surgical possibilities comprises modification of a deep inferior epigastric perforator (DIEP) flap breast reconstruction to facilitate additional autologous lymph node transplantation (ALNT). During this procedure, several vascularized lymph nodes from the inguinal region were included in the free abdominal skin flap and transferred to the affected axilla.[5] The symptoms of lymphedema were improved through an unknown method of action. The excess lymph fluid from the edematous extremity was possibly drained either through intra-flap lymphatic-venous connections, by lymphangiogenesis induced by the transferred flap, or a combination of both.[1, 4]



Most of the difficulties faced during surgery concern the intraoperative identification and preservation of the lymphatic nodes and vessels. Computed tomography angiography (CTA) can be used to localize and quantify the distribution of the lymph nodes in the inguinal area.[6] In our earlier work, we proposed a novel method of creating a virtual DIEP flap planning based on CTA, and projecting this information on the patient's abdomen. [7] The three-dimensional (3D)-reconstructed DIEP flap planning can be further elaborated by also indicating the locations of lymph nodes before surgery.

The aim of this paper is to share our clinical experience regarding the addition of lymph nodes into the virtual DIEP flap planning and projecting this information using a self-aligning pico laser projector onto the patient's skin to guide the surgeon towards the location of inguinal lymph nodes.

## METHODS AND MATERIALS

Between January and June 2015, a total of 10 patients underwent a deep inferior epigastric perforator breast reconstruction with a vascularized lymph node transfer. All patients followed the standard imaging protocol which consisted of a preoperative CTA to determine deep inferior epigastric artery vascular quality and its perforator locations.

Patients were scanned with a Toshiba Medical Systems Aquilion One 320 slice CT scanner. Using VitreaAdvanced fX Workstation (Toshiba Medical Systems, Europe), the intramuscular trajectory of the deep inferior epigastric artery and its branches towards perforators were highlighted. All significant perforators (diameter ≥1 mm) were annotated with yellow arrows perpendicular to the CT table and purple arrows to represent the most favorable perforators for transplantation. Additional to this planning, all lymph nodes in the inguinal area and the superficial circumflex iliac artery were reconstructed in the Vitrea software with little extra effort (figure 1).

To achieve global orientation of the highlighted anatomical features, four landmarks were indicated in the 3D reconstruction. These landmarks were the symphysis, bilateral spina iliaca anterior superior, and the umbilicus. At these exact locations, black and white markers were temporarily placed on the patient's landmarks (figure 2a). Using an in-house developed projection device, the projected CT data were automatically aligned to the indicated landmarks and displayed on the patient through a laser projector. The projected image was traced with a marker pen to be used as a visual reference during surgery in order to find not only the deep inferior epigastric perforators but also the lymph nodes hidden in the subcutaneous fat (figure 2b).

A modified technique of harvesting the inguinal flap originally described by Sulo et al. was used.[8] Besides indicating lymph nodes through projection, 0.5 ml of Patent Blue (ACROS Organics, Geel, Belgium) was injected intradermally into the lower abdominal wall above the iliac crest 10 min before the first skin incision. Dissection was initiated laterally with the deep inferior epigastric artery perforator flap. The superficial circumflex iliac artery (SCIA) was identified laterally and followed by the harvest of a fat flap from the inguinal area around the SCIA including tissue under Scarpa's fascia. The dissection was always limited to the level of the femoral artery. We included only the first palpable lymph node surrounding the SCIA pedicle into the flap. The lymph node was intraoperatively identified by the operating surgeon through touch and Patent Blue visualization, if possible. By pushing an instrument outward, such as a needle or finger perpendicular to the found node, the marked location could be reviewed (figure 3). The projected and marked location was deemed acceptable if the intraoperative lymph node was found within a radius of 1 cm from this position. For all patients, the surgeon's opinion was recorded and reviewed on the accuracy of the lymph node localization for all patients. After the lymph node flap dissection, the DIEP flap was raised in a normal manner.

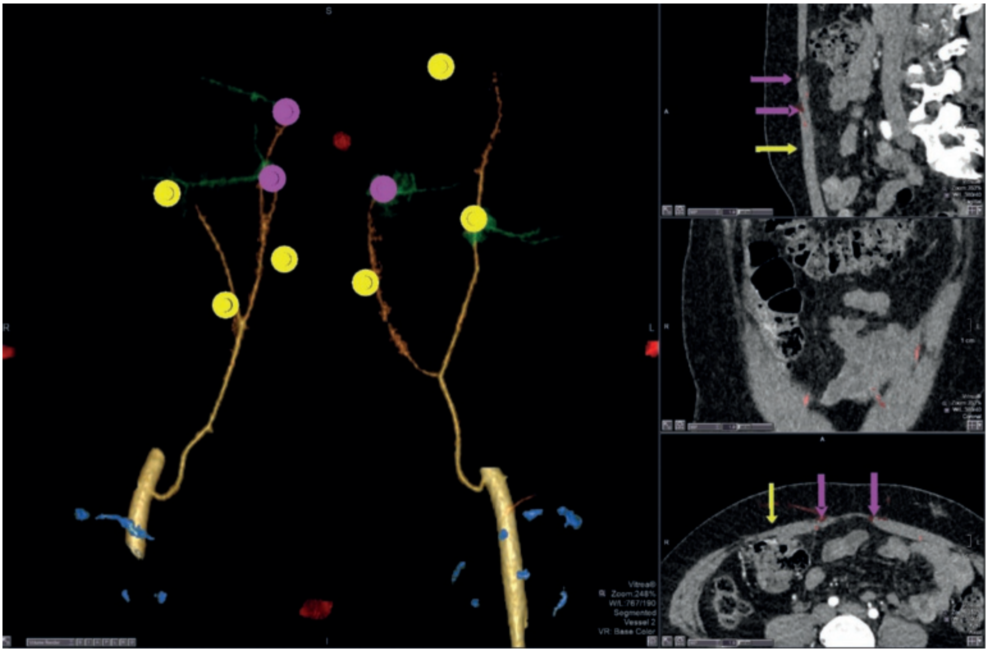


**Figure 1:** 3D reconstructed deep inferior epigastric artery and annotated perforators (yellow and purple arrows) with their subcutaneous branching pattern (green). Anatomical landmarks are displayed in red and lymph nodes in blue.

**a** **b**

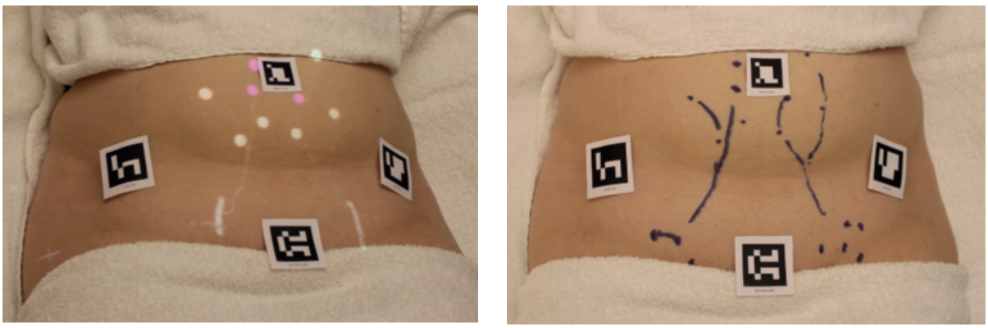


**Figure 2:** a) Markers placed on patient landmarks, image being projected from a self-aligning handheld projection device. b) After tracing of the projected image. Note the locations of lymph nodes in the inguinal area.

a b

**Figure 3:** a) Finger pushing upwards perpendicular to the found lymph node, corresponding with a marked location. b) Dissected vascularized lymph flap arranged for its natural position; earlier located lymph node indicated by surgeon.

**Table 1.** Overview of breast reconstruction patients with autologous lymph node transplantation (ALNT).

| Case no. | Age (yr) | Ablatio | Edema side | Edema Stage [9] | Therapy | Number of transplanted lymph nodes | Deviation projection vs reality (mm) |
|---|---|---|---|---|---|---|---|
| 1 | 53 | 2010 | Left | II | Unilateral DIEP with ALNT | 1 | 5 |
| 2 | 49 | 2011 | Left | II | Bilateral DIEP with ALNT left | 2 | 3 & 6 |
| 3 | 63 | 2012 | Left | II | Unilateral DIEP with ALNT | 1 | 5 |
| 4 | 53 | 2012 | Left | II | Unilateral DIEP with LV shunt & ALNT | 2 | 3 & 5 |
| 5 | 34 | 2013 | Left | II | Bilateral DIEP with ALNT left | 1 | 4 |
| 6 | 32 | 2013 | Right | II | Unilateral DIEP with ALNT | 1 | 0 |
| 7 | 47 | 2010 | Left | II | Unilateral DIEP with ALNT | 1 | 3 |
| 8 | 46 | 2009 | Left | II | Unilateral DIEP with ALNT | 2 | 0 & 3 |
| 9 | 54 | 2011 | Left | I | Bilateral DIEP with ALNT left | 1 | 5 |
| 10 | 47 | 2013 | Left | II | Bilateral DIEP with LV shunt left & ALNT | 1 | 0 |

## RESULTS

Inguinal lymph nodes were preoperatively projected and traced with a marker pen in a total of 10 patients. All patients were found intraoperatively to have preoperatively indicated lymph nodes within a one centimeter radius of the marking on the skin by the two operating surgeons

The recorded opinions of the surgeon indicated that harvest of the lymph node flap could be altered towards a more direct approach instead of conservative converging technique intraoperatively. Lymph nodes were located in the subcutis more conveniently, and surgeons felt that less tissue could to be dissected before harvest by doing so.

## DISCUSSION



Intraoperative localization of inguinal lymph nodes is a difficult task for surgeons, as these nodes are concealed in the subcutaneous fat. During surgery, available products such as Patent Blue may not migrate to all lymph nodes in the inguinal area. As a result, large harvested inguinal flaps have been described in literature in order to include sufficient lymph nodes. Excessive flap volume transfer contributes to the postoperative donor site morbidity such as seroma, hematoma, and edema, and care should be taken to harvest adequate tissue volume. Imaging modalities, such as ultrasound, are capable of preoperative lymph node visualization, but require a change in clinical workflow. Without any addition to our standard imaging protocol using CTA, we have developed a method to intraoperatively provide aid in lymph node localization. Besides pinpointing the inguinal nodes, the described technique shows potential in preoperatively planning the number of lymph nodes to be harvested, as well as determining the total flap volume. More research is warranted on more patients in order to quantify the clinical outcome regarding donor-site morbidity and relief of lymphedema-induced symptoms using preoperative lymph node planning.

The collected data were based on the expert opinions of the surgeons as quantitative intraoperative measurements proved to be challenging. Lymph nodes are located in the subcutaneous fat which must be prepared away from the skin, causing the lymph node flap to move around freely. Few landmarks (such as the umbilicus used for DIEP flap measurements) can be used in the sterile surgical inguinal area to act as reference. Using an instrument or finger proved the most convenient to estimate the accuracy of the marked lymph node in an already-lengthy operative procedure. We deemed expert surgeon opinion reliable as vascularized lymph node flaps were harvested on clinical experience and insight.

Further additional research should assess whether additional preoperative lymph node planning consequently leads to differences in clinical outcome, complications, or surgery time. With advances in medical imaging software, the total fat volume and lymph nodes to be transplanted from the groin can be calculated based on the CT data. Steps to integrate the prediction of these parameters into a virtual surgical planning in the future can consequently achieve optimal results for both the recipient and donor site.

## CONCLUSION

In this paper, we presented our experience with virtual planning of lymph node transplantations in a deep inferior epigastric artery perforator flap breast reconstruction. Based on the surgeon's expert opinion, this additional visual support aids in locating the lymph nodes in the inguinal area. Including the lymph nodes into the virtual planning of the flap and projecting this planning onto the patient is feasible and can be easily implemented in practice. Less tissue may be dissected in order to identify suitable lymph nodes, and a decrease in vascularized lymph node flap volume could be harvested, possibly reducing postoperative donor-site morbidity.

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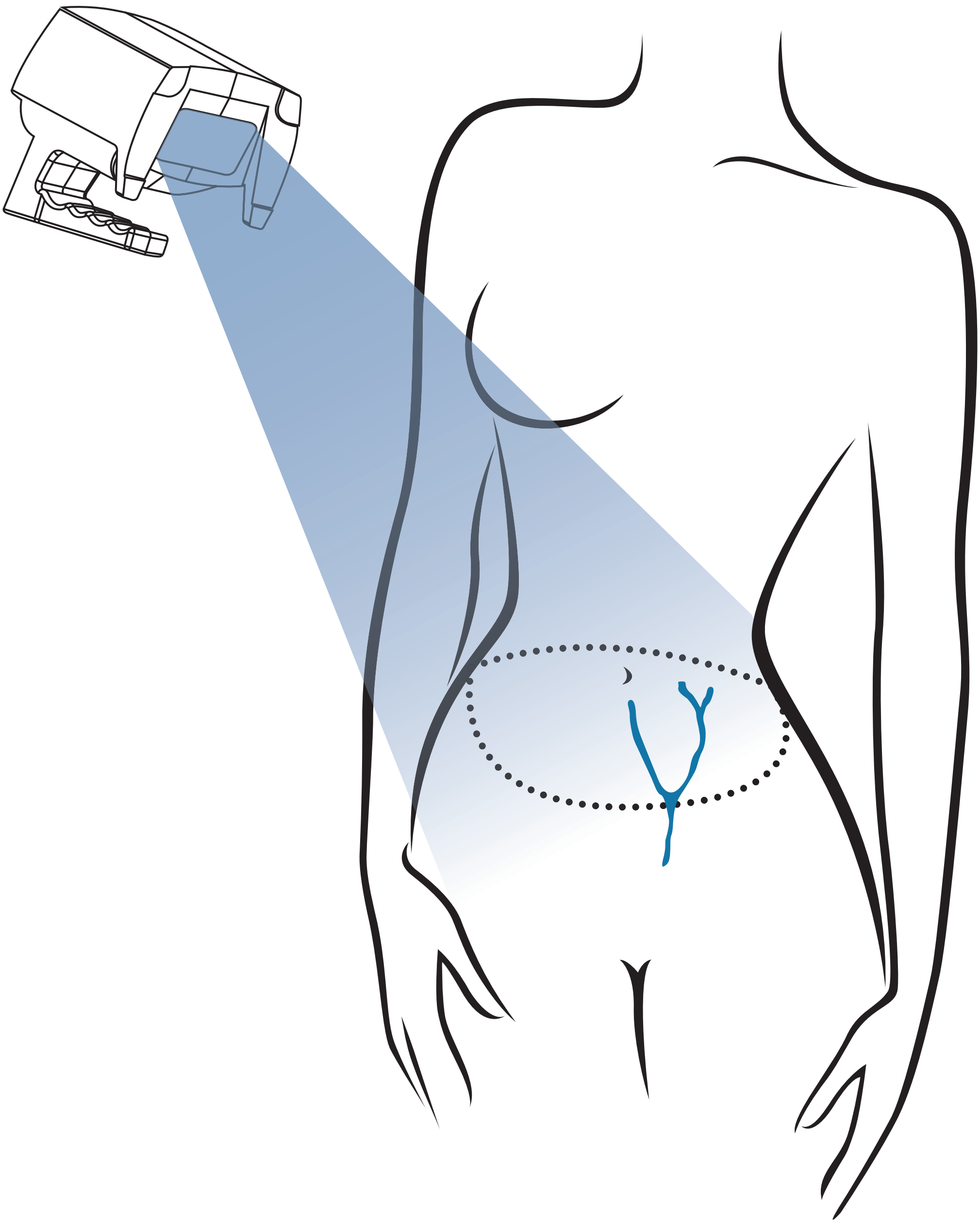
# CHAPTER 6

## An innovative method of planning and displaying flap volume delineations additional to perforator mapping to achieve symmetric breast volumes in DIEP flap breast reconstructions



# ABSTRACT

Determining the ideal volume of the harvested flap to achieve symmetry in deep inferior epigastric artery perforator (DIEP) flap breast reconstructions is complex. With preoperative imaging techniques such as 3D stereophotogrammetry and computed tomography angiography (CTA) available nowadays, we can combine information to preoperatively plan the optimal flap volume to be harvested. In this proof-of-concept, we investigated whether projection of a virtual flap planning onto the patient's abdomen using a projection method could result in harvesting the correct flap volume.

In six patients (n = 9 breasts), 3D stereophotogrammetry and CTA data were combined from which a virtual flap planning was created comprising perforator locations, blood vessel trajectory and flap size. All projected perforators were verified with Doppler ultrasound. Intraoperative flap measurements were collected to validate the determined flap delineation volume.

The measured breast volume using 3D stereophotogrammetry was 578 ± 127 cc; on CTA images, 527 ± 106 cc flap volumes were planned. The nine harvested flaps weighed 533 ± 109 g resulting in a planned versus harvested flap mean difference of 5 ± 27 g (flap density 1.0 g/ml). In 41 out of 42 projected perforator locations, a Doppler signal was audible.

This proof-of-concept shows in small numbers that flap volumes can be included into a virtual DIEP flap planning, and transferring the virtual planning to the patient through a projection method results in harvesting approximately the same volume during surgery. In our opinion, this innovative approach is the first step in consequently achieving symmetric breast volumes in DIEP flap breast reconstructions.

## INTRODUCTION

In autologous breast reconstructions, the deep inferior epigastric artery perforator (DIEP) flap is our preferred method for women with sufficient subcutaneous abdominal tissue as it provides satisfactory aesthetic results for the patients. [1-4] The abdominal subcutaneous tissue and its vascularization are transferred to the chest and moulded into a new breast. In general, the shaping of the transferred flap can be divided into two steps: obtaining correct flap volume and flap shape as basis for the correct conus and footprint of the reconstructed breast. [5] Currently, this process relies on mere visual estimation by the operating surgeon of breast size and shape for symmetric results. Artistic insight and skill are needed in shaping and selecting the ideal flap tissue volume to have an aesthetically pleasing breast reconstruction, which can, however, still be difficult even for the most experienced surgeons. [6]

The breast volume can be obtained utilizing water displacement techniques or mastectomy weight or by acquiring a preoperative 3D surface model of the patient's torso through 3D stereophotogrammetry. [7-16] Furthermore, since computed tomography angiography (CTA) is performed in each patient to identify perforator locations, preoperative abdominal adipose tissue volume information is available as well. [17-19] The approach of using subcutaneous fat volume information for planning the optimal flap has been increasingly described in the literature. [20, 21]

With these preoperative imaging techniques becoming more available nowadays, we combined the information of the preoperative breast volume and donor site tissue volume to preoperatively plan the optimal flap volume to be harvested. The general estimation of flap volume and the fat distribution within the donor site may facilitate in the harvesting of the donor tissue. In this proof-of-concept we elaborated our virtual DIEP flap planning method with flap volume delineations and investigated whether the preoperatively planned flap volume could be harvested accurately using our previously reported projection method. [22, 23]

## METHODS AND PATIENTS

In total, nine breasts were reconstructed in six patients (mean age 57 years). These patients underwent unilateral (n = 3 patients) or bilateral (n = 3 patients) DIEP flap breast reconstruction in a direct (n = 3 breasts) or delayed (n = 6 breasts) setting. All patients followed our hospital's standard preoperative imaging protocol, which consisted of 3D stereophotogrammetry (3dMD Body, 3dMD LLC, Atlanta, USA) and a preoperative Computed Tomography Angiography (CTA) using a Toshiba Medical Systems Aquilion One 320 slice CT scanner to determine deep inferior epigastric artery vascular quality and its perforator locations, which is gold standard. [18, 24]

Virtual computer model processing software (3ds Max, Autodesk Inc., USA) was used to interpolate the dorsal delineation of the virtual breast model obtained through 3D stereophotogrammetry. This allows the virtual separation of the individual breast from the patient's torso for further processing and volume analysis. In unilateral reconstructions or in the case of pathology, the contralateral breast was used for volume measurements.

On a VitreaAdvanced fX workstation (Vital Images, Toshiba Medical Systems, Europe), a virtual 3D planning containing the intramuscular trajectory of the deep inferior epigastric artery and its perforators was created. Consecutively, the patient's abdominal fat and skin were segmented semi-automatically using the workstation's built-in functions. Delineating the global outline of the DIEP flap was performed manually on the anterior–posterior aligned 3D model as displayed on the workstation by the operating surgeon. Within the global outline of the DIEP flap, guidelines indicating the desired volume to be transplanted as breast mound were created. These guidelines were added to the previously described perforator map planning (figure 1).

To transfer the virtually created planning onto the patient, an in-house developed device was used.[22, 23] In supine position, black and white markers were temporarily placed on four anatomical landmarks: the umbilicus, symphysis, and bilateral anterior–superior iliac spines. The projection device automatically aligns the virtual DIEP flap planning based on the markers and projects the planning onto the patient (figure 2). The preoperatively projected image is traced with a marker pen and validated with the use of handheld Doppler US for audible signals at the projected perforator locations (figure 3). After projecting the global outline of the DIEP flap, modification was possible, e.g., to ensure the scar would be hidden in a natural skin fold or to minimize dog-ear formation. However, no significant modifications were made to the outlines.

Intraoperative measurements were collected on weight of the harvested flap after trimming of excess tissue along the guidelines but prior to de-epithelialization. The density of adipose tissue is approximately 0.90 g/ml where the skin and blood have a density of approximately 1.1 g/ml; the density of the harvested flap was determined at 1.0 g/ml. [10, 25]

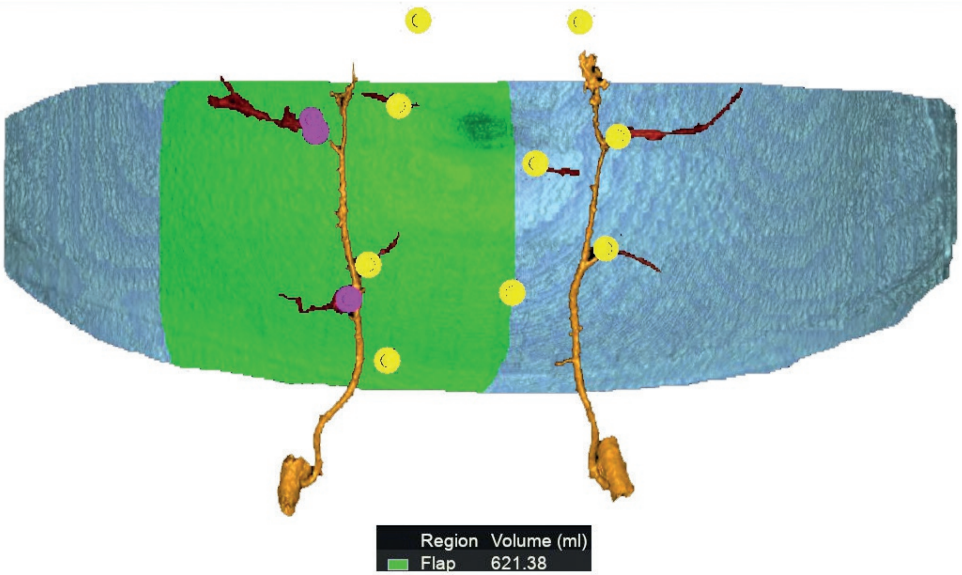



**Figure 1:** The virtual DIEP flap planning depicting the deep inferior epigastric artery and its subcutaneous branching. Yellow dots represent all significant perforators; purple dots are the most suitable for transplantation. The planned breast volume is in green.

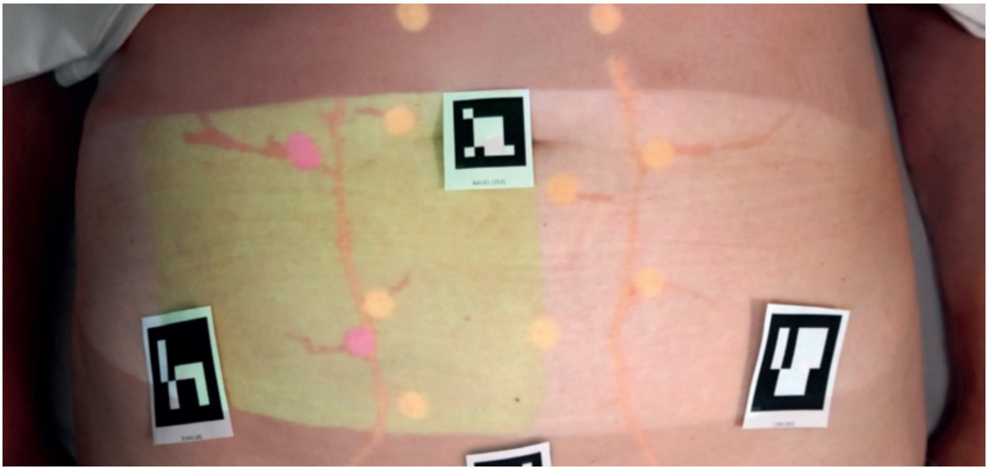


**Figure 2:** The virtual DIEP flap planning is projected in supine position onto the patient's abdomen. Black and white markers are temporarily placed on the patient's landmarks.

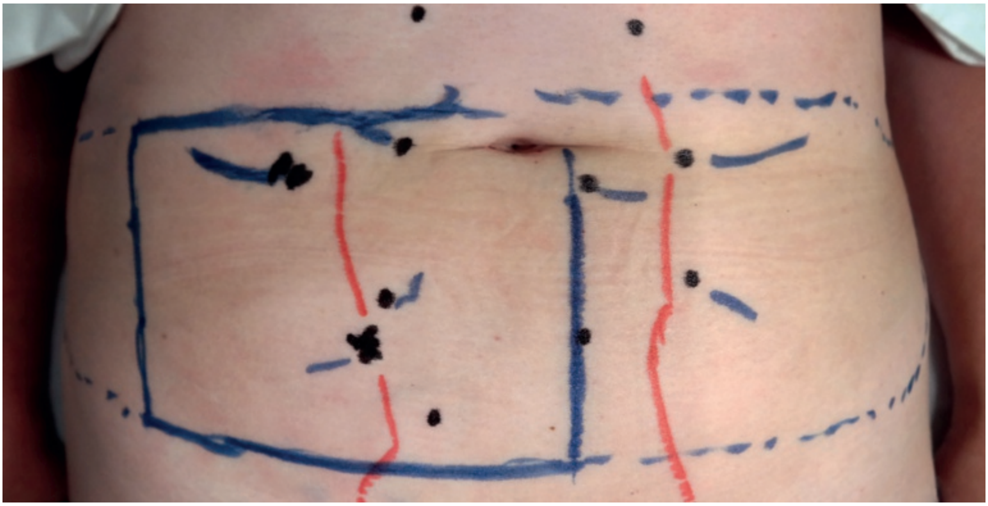


**Figure 3:** The traced virtual DIEP flap planning on the patient's abdomen.

## RESULTS

In the six patients who underwent breast reconstruction, all nine breasts were reconstructed without any intraoperative complications. A Doppler signal was audible in 41 out of the 42 projected perforator locations (98%). The harvested flaps (n = 9) weighed 533 ± 109 g on average. The mean difference between planned and harvested flap weight was 5 ± 27 g. Results are shown in table 1. Images of the preoperative situation and one month postoperative follow-up of case 4 can be seen in figure 4.

**Table 1.** Overview of planned and harvested volumes in breast reconstruction patients.
(*) the density of the harvested flap was determined at 1.0 g/ml.

| | | | | | Volumes (cc) | | | |
|---|---|---|---|---|---|---|---|---|
| **Case** | **Age** | **Setting** | **Side** | | **3D photo** | **CTA** | **Harvest *** | **Difference** |
| 1 | 54 | Delayed | Bilateral | Left | 500 | 486 | 505 | +19 |
| | | Delayed | | Right | 500 | 531 | 537 | +6 |
| 2 | 66 | Direct | Bilateral | Left | 600 | 453 | 503 | +50 |
| | | Delayed | | Right | 600 | 460 | 473 | +13 |
| 3 | 54 | Delayed | Unilateral | Right | 800 | 773 | 770 | -3 |
| 4 | 41 | Direct | Bilateral | Left | 425 | 456 | 427 | -29 |
| | | Direct | | Right | 425 | 467 | 428 | -39 |
| 5 | 62 | Delayed | Unilateral | Left | 700 | 500 | 513 | +13 |
| 6 | 64 | Delayed | Unilateral | Left | 650 | 621 | 640 | +19 |
| | | | | **Mean** | 578 | 527 | 533 | +5 |
| | | | | **Standard deviation** | 127 | 106 | 109 | +27 |

6

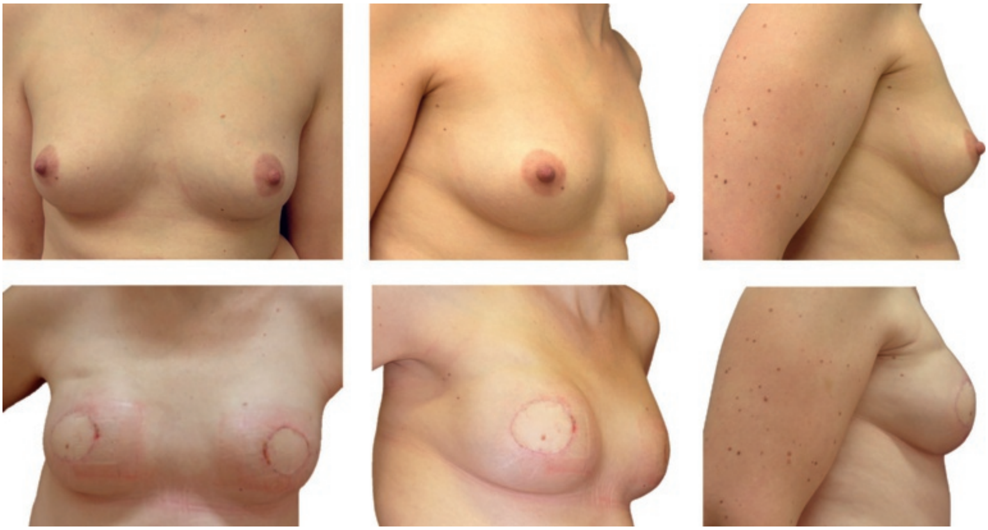


**Figure 4:** Preoperative and 1-month postoperative photos of case #4.

## DISCUSSION

Our standard preoperative documentation procedure already consists of 3D stereophotogrammetry for estimation of the breast volume, as well as CTA, on which we create a virtual 3D perforator planning. Creating the virtual planning and projecting this onto the patient was performed in less than 20 minutes, requiring only minor modifications to our standard preoperative protocol. We are aiming on making the in-house developed anatomy projector widely available, providing this user-friendly technique to more health care centers.
Losken et al. reported that the variability in volume measurements deviate on average between 13% and 16% of the actual breast volume when using 3D stereophotogrammetry.[13] More research is needed into the validity and accuracy of the measured breast. Hence, the planned flap volume was considered as a guideline, meant to aid the surgeon in decision-making.

Flap delineation of the 3D model, based on CTA data, was performed manually by tracing the contours on the workstation. Virtually adding and subtracting abdominal fat to the flap gives a convenient method of creating the correct shape and size of the flap.

The distribution of fat within the reconstructed breast can be planned in such a manner that the natural adipose tissue surplus located medially in the DIEP flap is optimally situated in the reconstructed breast. This preoperative process may decrease surgery time, as the decision-making can be performed in a virtual environment. The patient can also be informed prior to surgery that insufficient tissue is available from the donor site and that her natural volume cannot be restored (e.g. in case 5) or consider her wishes for different breast volumes.

Upon virtual planning, one should try to conceal the donor site scarring within natural skin folds, as often can be seen in a rendered 3D reconstruction of the skin. Furthermore, it is of importance that the CTA used for planning is fairly recent, as abdominal adipose tissue is subject to changes when the patient is actively losing or gaining weight prior to surgery. In addition, the contour of the lower abdomen should not be deformed by the patient's hands or clothing, as these may negatively influence volume calculations and distort natural skin folds.

The total number of patients in the study was modest, and both uni- and bilateral breast reconstructions were included either in a direct or delayed reconstruction setting. However, as a proof-of-principle, we deemed the variety and size of the study population acceptable.

Clinical outcomes and implications are yet to be determined in a larger study group with prolonged follow-up to assess the morphological changes of the breast over time.

Future research will also focus on preoperatively planning the blueprint for the desired cone shape of the breast. Unilateral breast reconstructions with stacked DIEP flaps for women with larger breasts may also benefit from this approach. The volume of each individual flap could be planned and depicted onto the patient while taking perfusion zones and intra-flap perforator locations into account. We aim to eventually transfer the correct volume and shape during the primary surgery to decrease the number of secondary corrections.



## CONCLUSION

This proof-of-concept shows in small numbers that it is possible to include flap volumes within a virtual DIEP flap planning with minimal effort, transfer the virtual planning to the patient through the projection method, and harvest the same volume during surgery. We believe that this innovative approach is the first step in consequently achieving symmetric breast volumes in DIEP flap breast reconstructions.

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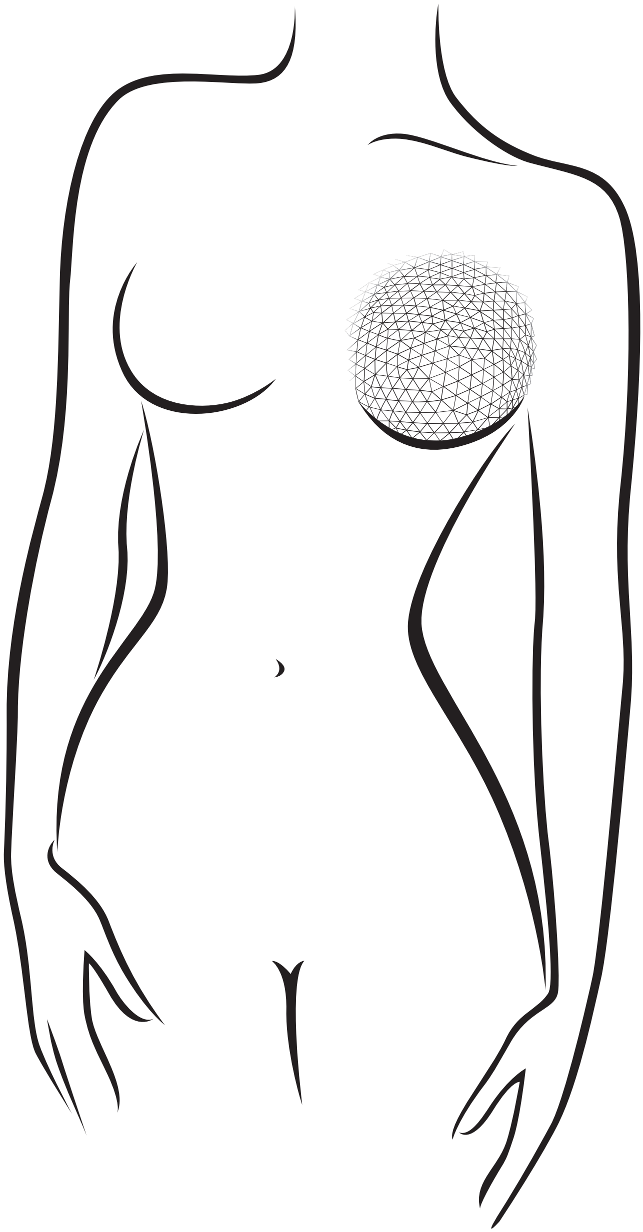
# CHAPTER 7

## Applications and limitations of using patient-specific 3D printed moulds in autologous breast reconstruction



## ABSTRACT

Over the last years, several techniques have been proposed to improve the outcome of autologous breast reconstruction procedures. One of these innovations describe patient-specific, three-dimensional (3D) printed breast moulds for intraoperative use based on 3D stereophotogrammetry. In this paper, we want to share our preliminary experiences with producing such templates, its clinical possibilities and limitations in practice, illustrated by three cases.

In this feasibility study, a total of six patient-specific templates were designed based on 3D stereophotogrammetry images. The 3D template was fabricated using a 3D printer. During breast reconstruction, the autologous flap was placed inside the printed template to aid the surgeon in determining the shape and volume of the autologous flap creating the desired breast dimensions.

Patient-specific breast templates are inexpensive and relatively easy to design, while being practical and convenient to obtain insight in the dimensions of the desired breast during reconstruction, according to the operating surgeons. Patient selection is however critical, as patients must have sufficient donor volume and/or satisfying breast shape to be able to use the template to its full potential.

## INTRODUCTION

Over the past decades, the number of breast reconstructions have greatly increased. For reconstructions using autologous tissue, the most commonly applied technique is the deep inferior epigastric artery perforator (DIEP) flap.[1] During this reconstruction, subcutaneous fat and skin from the lower abdomen is transferred as a vascularized free flap to the torso in order to reconstruct the breast.[2] Another method in autologous breast reconstructions is the profunda artery perforator (PAP) flap, where tissue from the inner thigh is transferred to the thorax to be modelled into a breast.[3] Obtaining an aesthetically pleasing breast reconstruction correlates with the composed conus and footprint of the reconstructed breast. Finesse and intuition are needed to harvest and establish the ideal flap shape and volume.[4] Providing aid in this process can be beneficial for both surgeon and patient.[5]

Pre-operative imaging for breast reconstruction procedures is gold standard in many medical centres. Amongst the imaging modalities is three-dimensional stereophotogrammetry (3D photography). Through this technique, several images of the subject are simultaneously taken using multiple photo cameras under various angles. As the angles between these cameras are known, the position of separate points on the subject's surface can be calculated, resulting in an accurate 3D surface model of the subject. Apart from elaborately and objectively documenting the patient's pre-operative status, extra information can be derived from these 3D images. Breast parameters can be objectively quantified and utilized prior to and during the breast reconstruction procedure, improving patient healthcare.[6-10]

Amongst the applications utilizing the information obtained through photographing breast, is the designing of patient-specific breast moulds to facilitate the surgeon in flap shaping.[11, 12] During the breast reconstruction procedure, the autologous tissue can be placed inside the template in such a manner that the flap adapts to the shape. If necessary, adjustments to the free flap can be made based on the template to match the dimensions of the desired breast. Such novel techniques may aid in to manage patient expectations and optimize breast reconstruction outcomes.

In this study, the design and application of templates produced with a 3D printer was investigated for feasibility in a pilot study for both immediate and delayed reconstructions, as well as unilateral and bilateral reconstructions. We share our methods for obtaining such 3D printed mould and our preliminary experiences of the clinical possibilities and limitations in practice, illustrated by three contrasting cases.

## METHODS AND PATIENTS

Six consecutive patients between 31 and 65 years old were included in this feasibility study. Three patients underwent an unilateral, delayed breast reconstruction and three patients received a bilateral reconstruction (one immediate, one delayed reconstruction and one delayed with the use of tissue expanders). All patients followed a standard preoperative imaging protocol which consisted of a Computed Tomography Angiography (CTA) scan for evaluation and 3D planning of perforators, and 3D photography of the torso for clinical documentation.[13, 14] 3D images of the torso were obtained using a commercially available multi-camera set-up, 3dMD Body (3dMD, Atlanta, USA). The system consists of four pods with a total of twelve cameras aimed at the patient's torso at various angles. During image acquisition, the patient was standing in front of the cameras with the hands positioned at the hips for reproducible results.[15] The associated software with the 3D stereophotogrammetry system automatically created a 3D surface model from the captured images. The computer model obtained through 3D photography was exported and loaded into 3D software Autodesk 3ds Max (Autodesk Inc., USA) to start the process of creating a 3D template to be used during breast reconstruction surgery.

In the case of an unilateral breast reconstruction, the contralateral breast was delineated and virtually isolated from the torso. After mirroring along the vertical axis, it was transposed to the affected site in the 3D software. Alterations to the edges of the virtually isolated breast were made to ensure the contours would follow the thorax wall. Theoretically, any modification to the virtual breast could be made at this point, such as a virtual ptosis reduction, which would be reflected in the 3D printed breast mould.

In the case of a immediate bilateral breast reconstruction, the most aesthetically pleasing breast was selected to be mirrored to the contralateral side for symmetry purposes following the same principles as the unilateral breast reconstruction 3D mould creation process. Theoretically, both breasts could be virtually isolated and produced into a breast template, if patient wishes to approach her natural asymmetry in the pre-mastectomy situation.
In the case of a delayed bilateral breast reconstruction, absence of a pre-operative 3D photographic model was encountered. No 3D preoperative information was available on breast volume or shape, as mastectomy had already been performed. In consultation with the plastic surgeon performing the breast reconstruction, a virtual breast was crafted suiting the patient's posture.

The finalizing steps of creating a breast mould for either breast reconstruction setting incorporated the ventral extrusion of the outer rim of the breast contour. This provides the breast mould to be placed on a flat surface in such a manner that the flap can be conveniently positioned inside the template. The template of the wall was thickened to four millimetres to providing sufficient strength during intraoperative use. The final step in virtually modelling the surgical breast template was to clean up and smoothen the 3D design. An general overview of the 3D printing design procedure is shown in figure 1.

The model was imported into 3D printing software Cura (Ultimaker B.V., the Netherlands), where support structures were added to prevent the model from collapsing during the printing process. The mould was printed with an Ultimaker 2 (Ultimaker B.V., the Netherlands) using Polylactic Acid (PLA) filament on default printer settings. After 3D printing of the template, the supporting material was removed manually.

Once in an operative setting, the 3D printed mould was placed in a sterile plastic sleeve to be used for the fitting of the free flap. Prior to anastomosis, the flap was positioned in this sterile covered template, where the contours of the free flap could be traced with a marker pen along the 3D printed mould, and sutures can be placed to maintain flap shape.

As part of standard photo documentation, 3D images were captured of all patients six to nine months post-operatively. Final breast volume and width on these images was assessed using Autodesk 3ds Max software.

To gain more insight into the possibilities and limitations of patient-specific 3D printed breast templates, three contrasting cases will be discussed further.



### Patient cases

Case one, aged 37, presented herself with a palpable malignant tumor in the right breast. She was diagnosed with BRCA gene mutation for which a bilateral, preventive ablation with direct subpectoral tissue expander placement was performed. In a later stage, the breast reconstruction would be completed via a DIEP flap. After completing the periodic filling of the tissue expanders, the final breast volume measured 490 cc each. As her breasts were asymmetrically positioned due to the prior surgery, the right breast formed the basis for the 3D printed templates.

Case two was predisposed with a BRCA-1 gene mutation for which a bilateral preventive ablation was planned along with a direct reconstruction. The PAP flap technique was selected for this 30 year old woman, as insufficient abdominal tissue was available. Although the patient was satisfied with her breast volume, she would like the ptosis of her breast to be altered.

Case three had undergone a unilateral breast-saving lumpectomy as a result of a tumour in the right breast when she was 49 years old. She presented herself with a retracted scar, displaced nipple, poor skin quality and lymphedema of her right arm after radiotherapy and chemotherapy. It was determined that she was eligible for a unilateral DIEP flap, alongside with a vascularized autologous lymph node transfer to be placed within the axilla.

## RESULTS

In six patients, pre-operative 3D photographs were taken on which a patient-specific 3D printed mould was designed to be used during the breast reconstruction. Six to nine months post-operatively 3D photographs were repeated in order to calculate the breast width and volume between of reconstructed breast. Patients who had unilateral reconstructions, a width difference of 0.5 cm and mean volume difference of 211 ml between the reconstructed breast and contralateral side was found. For bilateral reconstructed patients a mean difference in breast width and volume of respectively 0.5 cm and 16 ml was found. Results of these postoperative measurements are shown in table 1.

### Patient cases

*Case 1*

After completing filling procedures, her tissue expanders contained 490 cc saline fluid. The expanders were removed and the expanded skin pocket was padded with the (partially) de-epithelialized DIEP flap. Clinical photos can be seen in figure 2. Nipple reconstruction and secondary corrections was performed at a later stage.

*Case 2*

The aim of this 3D printed mould was to recreate the patient's breast shape prior to ablation. In consultation with the operating surgeon no modification was made to the 3D printed mould, despite the mild upper pole volume defect. As per patient request, the required upper pole volume was increased intraoperatively by surgeon experience. The preoperative situation and six month post-operative breast reconstruction results are shown in figure 3 prior to nipple reconstructions.

*Case 3*

A 3D printed template was produced for the harvested flap, based on mirroring of the contralateral side. However, total flap volume to be obtained from the donor site proved to be insufficient. In a secondary procedure, breast volume was increased through lipofilling, additionally, the contralateral breast was reduced and lifted. Due to insufficient donor site volume, the 3D printed mould was of little added value for volume assessment in this case, and was used for determining the width and placement of the breast reconstruction. Photos of the reconstruction result prior to the second symmetrising procedure can be found in figure 4.

**Table 1:** Breast volumes and breast widths derived from 3D stereophotogrammetry six to nine months after surgery with utilization of the 3D printed template.

| | | Volume (cc) | | | Width (cm) | | |
|---|---|---|---|---|---|---|---|
| **Case** | **Reconstruction** | **Left** | **Right** | **Difference** | **Left** | **Right** | **Difference** |
| 1 | Bilateral | 619 | 603 | 16 | 20 | 19 | 1 |
| 2 | Bilateral | 279 | 263 | 16 | 16 | 16 | 0 |
| 3 | Right | 580 | 864 | 284 | 18 | 18.5 | 0.5 |
| 4 | Bilateral | 420 | 403 | 17 | 19 | 19 | 0 |
| 5 | Right | 803 | 620 | 183 | 19.5 | 19.5 | 0 |
| 6 | Left | 462 | 629 | 167 | 17 | 18 | 1 |

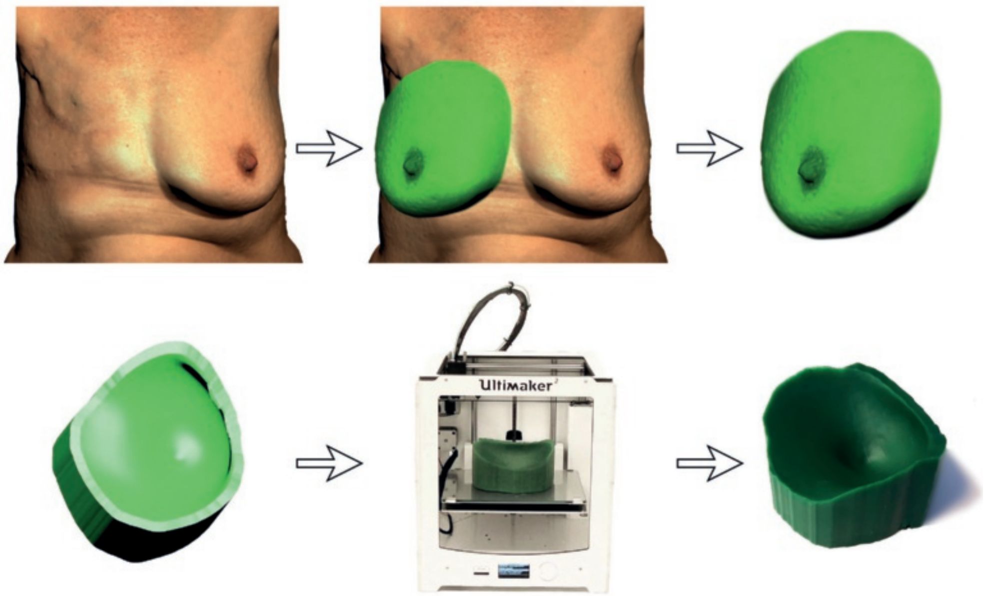



**Figure 1:** Design of a patient-specific template for an unilateral breast reconstruction. The contralateral breast is virtually isolated and mirrored based on 3D photography. Extrusion of the outer rim of the virtual breast provides a flat base. Finally, the design is printed using a 3D printer.

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**Figure 2:** Case 1.Status after bilateral preventive ablation with completed tissue expanders filling.
Left: Tissue expander in situ prior to DIEP flap reconstruction.
Right: Nine months after DIEP flap reconstruction, prior to secondary corrections.

**Figure 3:** Case 2. Bilateral preventive ablation with a direct breast reconstruction using the PAP flap technique.
Left: Preoperative situation with mild volume defect in the upper pole.
Right: Six months after PAP flap reconstruction, prior to secondary corrections.

**Figure 4:** Case 3. Unilateral DIEP flap reconstruction with insufficient donor site volume.
Left: Preoperative situation after lumpectomy, radiotherapy and poor skin quality.
Right: Six months after DIEP flap reconstruction, prior to secondary corrections.

## DISCUSSION

Our preliminary clinical experience with the usage of patient-specific 3D printed breast moulds have been described in this paper and illustrated by three diverse clinical cases. Using already available techniques and equipment, 3D printed breast templates were created for patients undergoing both unilateral and bilateral breast reconstructions.

In this feasibility study, the post-operatively recorded breast volumes and width varied between patients. In the three bilateral breast reconstructions, minimal post-operative breast volume difference between the reconstructed breasts was measured. The three unilateral reconstructions showed however a substantial deviation in breast volume between both breasts, as either the patient had insufficient donor site volume, or her wishes were to get a ptosis reduction in the contralateral side. In all unilateral patients secondary corrections of the contralateral breast were performed to get a more symmetric results.

For the template to be utilized to its full potential, patient selection for the creation of 3D printed breast moulds is crucial. Patients should be satisfied with their natural breasts, or unaffected side. An adequate amount of adipose tissue should be obtainable from the donor site. By preoperatively comparing fat volume measurements on the preoperatively performed CTA scan with breast volume measurements derived from the 3D photo, one can acquire insight in whether the desired volume can be reached within one procedure. Additionally, in case of a greater surplus of the donor site compared to the breast volume, a cover on top of the 3D printed breast template could be beneficial to encapsulate the total breast shape.



Unilateral breast reconstruction patients may have a tissue expander in situ. When designing a 3D printed breast mould, it should be noticed that the expanded breast pocket may not correlate with the shape of the natural breast. Measuring the total breast volume and subtracting the volume injected into the tissue expander can provide information regarding the thickness of the mastectomy skin flap. When mirroring the contralateral side design steps can be taken into consideration to correct for locally present volume from the expanded mastectomy flap. To manage patient expectation, one may even speculate on the idea that in consultation with the patient and plastic surgeon the breast reconstruction is virtually shaped, of which a mould is printed.

In both unilateral and bilateral delayed breast reconstructions, multiple factors are at play when determining the final shape of a reconstructed breast. The thickness of the mastectomy flap and quality of the skin pocket are of essence in the decision regarding how the reconstruction should be performed. The skin paddle from the autologous flap is de-epithelialized and trimmed to replace the native skin of insufficiently quality by donor skin from the autologous flap. How much skin paddle should be utilized in autologous flap reconstruction should be determined prior to placement of the flap in the breast mould, as the overall contour and shape of the reconstructed breast are influenced by these decisions.

The technique of 3D stereophotogrammetry is part of standard clinical workup for all our breast reconstruction patients. Also, an Ultimaker 2 was already available in our hospital for research purposes. The template was designed within 15 minutes and printing time was about 16 hours, costing around 20 euro. Using a sterile sleeve as protective packaging instead of a sterile printed mould is more economical, without being impractical during surgery. The Autodesk 3ds Max software used for creation was available as already available license to our department; however, free alternative software such as MeshMixer (Autodesk Inc., USA) can also be used for the purpose of designing 3D models. Therefore, this research was conducted without purchasing additional hardware, minimizing the total added cost for this innovation in autologous breast reconstruction.

According to surgeon's opinion, 3D printed breast templates could be a useful tool during the operation for assessing the flap volume, shape, and orientation. They expressed it was convenient in practice and aided in visualizing the final shape of the reconstructed breast. Especially less experienced surgeons may benefit from the usage of the proposed 3D printed template. The most potential of this technique would lay in unilateral patients who are satisfied with the shape of their unaffected breast and have adequate donor site volume. In bilateral reconstructions a symmetric breast reconstruction may be obtained more conveniently. These hypotheses would need to be tested in a larger study. Future studies will focus on clinical outcomes such as patient satisfaction, surgery time, breast volume, size and symmetry between breasts within a larger, patient-selected population. As design and printing can be done relatively quickly at low costs, only a minor improvement in outcome would already result in a cost-effective clinical tool.

## CONCLUSION

Recreating the female breast in an autologous reconstruction requires insight and skill. Through 3D stereophotogrammetry and 3D printing, a patient-specific template can be created, supporting the surgeon in the intra-operative decision making of breast shaping. Creating the breast template can be done at low costs and relatively fast. For both unilateral and bilateral breast reconstructions, in a direct or delayed setting, a breast mould could be considered as a useful and cheap addition to the autologous breast reconstruction procedure. However, if the patient has insufficient donor site volume available, or is unsatisfied with the appearance of her natural breast, the process of fabricating a 3D printed template is of little added value. Therefore patients should be pre-selected for utilizing this technique.

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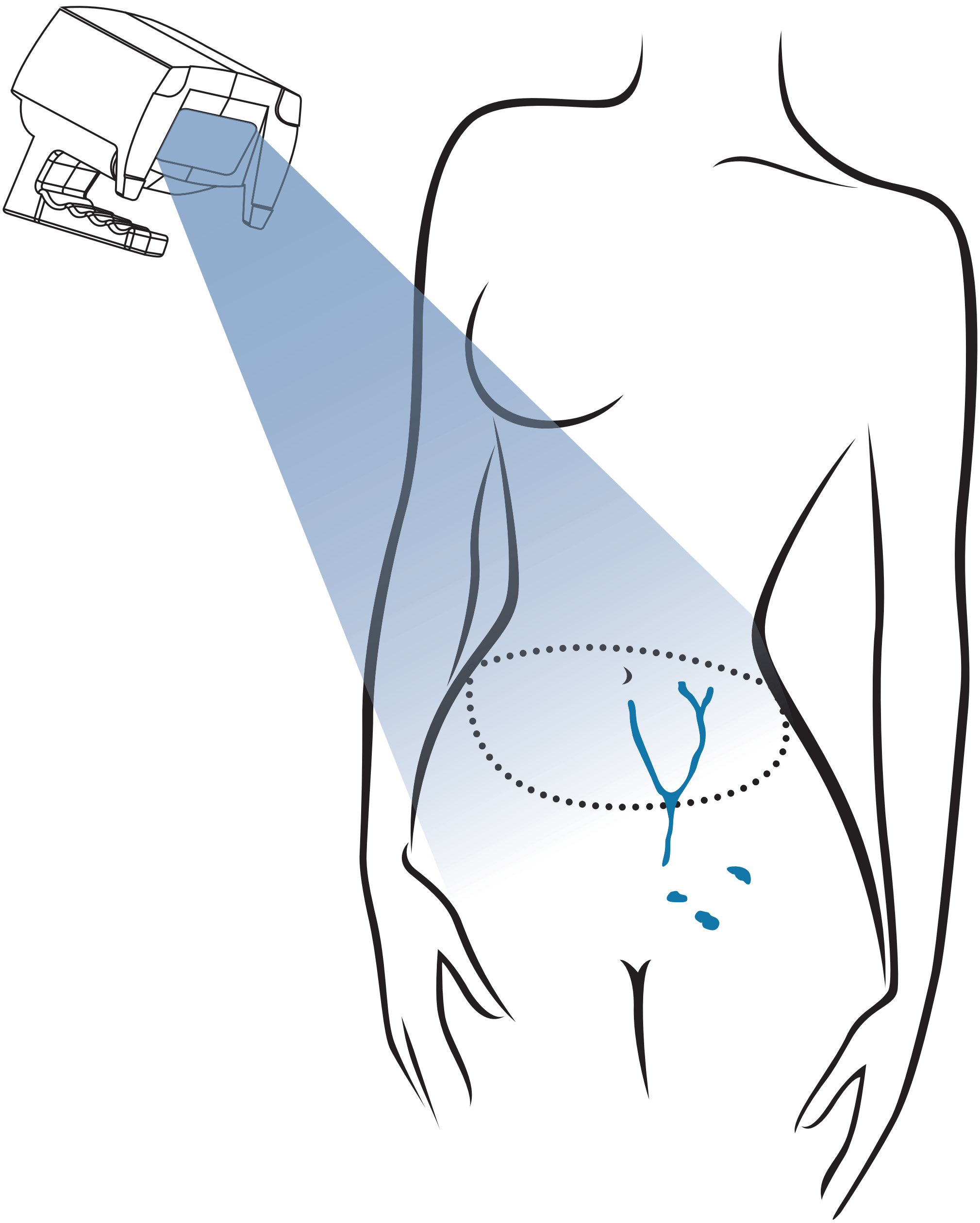
# CHAPTER 8

## General discussion and future prospects



This thesis illustrates the development and application of innovations in breast reconstructive surgery. Novel ideas and techniques are essential in the continuous strive to improve patient care. Whereas breast reconstructions in the 80's mainly focused on restoring, patients nowadays also expect aesthetically pleasing results. The public is well-informed regarding the various available options. Images of breast reconstruction outcomes are readily available on the internet, and it is of importance to manage patients' expectations regarding symmetry, volume, shape and scarring. [1, 2] In order to inform patients and provide the best care, modern-day health care professionals have increasingly more tools at their disposal, including state-of-the-art imaging and post-processing techniques. Breast implant selection can be aided by the use of 3D photography providing information to both the patient and the surgeon.[3] In cases of autologous reconstructions, the free flap can be planned, incorporating the vascular anatomy, perforator locations, lymph node distribution and flap volume, which provides the surgeon with more information than previously available.

However, the major downside remains the fact that these advanced virtual planned 3D models are only displayed onto a computer screen. The translation from computer model, as seen on a monitor, to the patient is done in the surgeon's head. The alternative of displaying a model onto a computer screen which is subsequently viewed for example by wearing virtual reality headsets has a major downside. From a practical standpoint, surgical loupes cannot be worn alongside such a headset. Furthermore, all visuals perceived by the wearer of the headset are computer generated and displayed on two miniature screens, one for each eye. Users are immersed in a virtual world, diminishing the possibility of actually seeing the patient. Aiming to bridge this gap, we developed a technique which ensures the carefully planned surgery is transferred directly from the computer model onto the patient without losing contact with reality. In this way the surgeon sees the planning displayed on the patient's skin. By doing so, augmented reality was introduced into breast reconstructive surgery. This takes away the necessity for the surgeon to look at monitors, thereby allowing the surgeon to focus on what matters most: the patient.



In our quest to meet patient demands and international benchmarks, we are driven to improve performance and clinical outcome. We need to perform at our best for our patients. An increasing number of procedures are being performed, leaving a footprint on the national health care budget. One way to reduce the procedural costs is by improving the efficiency of a procedure, e.g. by lowering surgery times, complications and hospital stay. Medical innovations may help in constraining the continuous growth in expenses. However, resources are easily consumed within a clinically driven innovation development project, and can prove to be unviable after years of development as insufficient prior research was performed to determine where it has the most added value. Methodologies such as health technology assessment should be embraced to assess whether and, if positive, where (surgical) procedures could be improved by technology. Within this research we focused on developing a prototype with sufficient performance to be able to show added value and feasibility upon improvement.

The prototype setup contains an external laptop which drives the graphics feed. This prototype could be miniaturized into a computer the size of a smartphone and embedded into the device itself. Automatic landmark detection of the patient is desirable, eliminating the placement of paper markers placed on the patient, the latter which could hinder the surgeon in an operative setting. Various modes could be implemented, such as dynamic projections to indicate blood flow, perfusion zones or lymph drainage direction. Finally, control of the projection system can be further improved, for example by allowing directive gestures by the surgeon to change the projection to highlight a specific part of the virtual planning.

These proposed improvements of the projector are mostly for user convenience and user environment. Such developments will increase the efficiency and efficacy. As we must remain cautious of our limited health care budget, this medical institution innovation should be further developed through, for example, a spin-off corporation or (exclusive) license collaboration and as such should be financed through external investments. Commercialization of this technique is therefore the designated path to follow. Patent applications have been filed in Europe and the United States to protect the developed intellectual property and to attract investors, and a STW Demonstrator subsidy has been granted to further develop the prototype.

Miniaturization of the anatomy projector technique has the benefit that it can be placed within an operating theatre to display the planning while the surgery takes place, thereby giving it the potential to be applied in standard practice for all breast reconstructive surgeries. Clearly, the technique has much more potential than just to display a 3D planning for breast reconstructions. We invite our colleague health care professionals to assess their procedures and to determine if their process can be improved by displaying a virtual surgical planning onto their patients.

Various other technologies have been developed over the last decade in order to provide better health care. Detectors, injectables, breast implants with chips and mobile apps have been proposed within breast reconstruction alone, ranging between pre-, intra and post-operative setting. For patients, e-Health solutions are available such as MediMapp (Soulve Innovations, Utrecht, the Netherlands) which provides a 'metro line'; all information regarding appointments, doctors and lifestyle after surgery can be reviewed within an smartphone app. For surgeons, thermal imaging techniques have been investigated to non-invasively gain insight in superficial perfusion locations pre-operatively. [4, 5] Furthermore, intra-operatively the vitality of the flap can be assessed using indocyanine green, an injectable dye. [6] Besides perfusion, the migration of lymph fluids can also be visualized through an ICG-system. [7, 8] Methods for continuously and remotely monitoring a flap post-operatively are being investigated and developed to ensure objective real-time measurements, allowing for faster detection of complications. [9] Also, the development of 3D printing techniques have accelerated over the last couple of years, increasing print quality, materials choice at decreased printing time and costs. It will only be a matter of time before a 3D printed biomaterial can be sufficiently vascularized as a suitable scaffold for autologous fat to act as a breast reconstruction, basically growing a new breast, possibly replacing the DIEP flap procedure altogether.[10]

Technological developments occur in quick succession. After more than 50 years, Moore's law is still applicable, stating computer power is doubled every two years. The exponential growth implies not only technology can be developed faster, but will also become more affordable. For example, infrared techniques have been greatly reduced in price; a smartphone infrared camera module is one tenth of the price of a regular infrared camera, allowing for faster access to technologies. That technology development is accelerating is evident. Without prior notice, the augmented reality glasses HoloLens (Microsoft, Redmond, USA) were introduced in 2016, which were initially designed for office applications and gaming industry. With an array of possible applications within health care, the crossover to this field seems obvious. In the same year, Google's artificial intelligence (AI) beat a professional player five out of five times at the Chinese game Go, an accomplishment not expected by experts for another decade. Key opinion leader Geoffrey Hinton (Google, working at artificial neural networks) predicted this year that artificial intelligence, derived through deep learning of big radiologic data, will replace a substantial number of radiologists in five to ten years. Embarking on this thought, the field of pathology could be next, as basically the same data-types are being processed and artificially predicted. These sudden improvements in technology over the last two years underline that we are far away from any medical technological plateau, and both anticipation and adaption to this new reality is key to remain innovative and disruptive in medicine.

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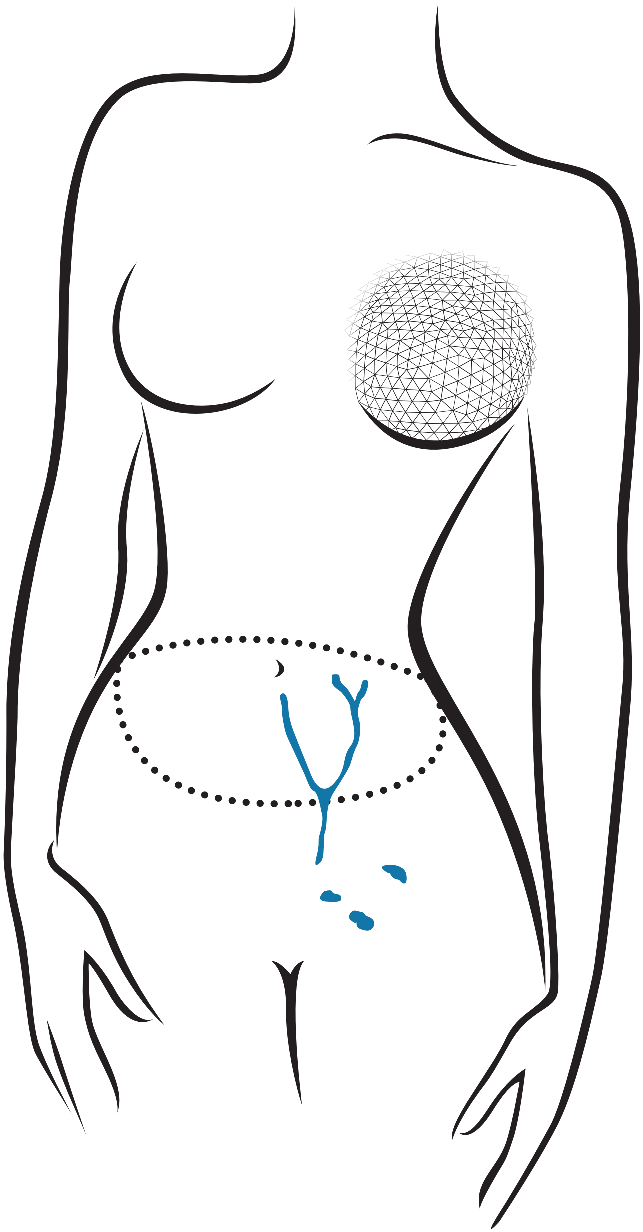
# CHAPTER 9

## Summary



In deep inferior epigastric artery perforator (DIEP) flap breast reconstructions, a free tissue flap consisting of adipose tissue, skin and supplying blood vessels is transferred from the abdomen to the thorax. The perforating blood vessels are millimetric and of great importance for the survival of the DIEP flap. Hence the location of these perforators should be identified pre-operatively to avoid accidental intraoperative destruction. With either handheld Doppler ultrasound (US) or computed tomography angiography (CTA) these perforators can be depicted. However, when selecting these blood vessels through CTA, the information remains on the computer screen for which a convenient method of transferring was required. The exploratory pilot study described in **chapter 2** was designed to investigate the hypothesis that by means of projection methods one can transfer a computer generated planning onto the patient. By utilizing a consumer pico video projector, one can display the image on the patient. To achieve correct scaling and rotation of the image, a ruler was placed on the patient's abdomen. The projected image was traced with a marker pen, and verified with Doppler US. To obtain a gold standard for perforator locations, intraoperative measurements were taken and compared with the preoperative projected locations. This rudimentary setup showed a significant improvement in localizing perforators, confirming the hypothesis.

As the primitive prototype would need further development for application in clinical practice, assessment of the potential added value of the innovation prior to further development and research phases was required. In **chapter 3**, a mathematical model of a bilateral DIEP flap breast reconstruction was created, capable of simulating the total room for improvement in financial terms (headroom analysis), various implications (scenario analysis) and decisions at various outcome and cut-off values (threshold analysis). The model indicated that there is room for improvement in a bilateral DIEP flap breast reconstructions, totaling €889 euro. Further modeling revealed that when surgery time is reduced by 15 minutes and complications by 50%, the innovation will remain cost-effective at €671 per patient.

In order to evaluate the actual impact in clinical practice, a single-center randomized controlled trial was set-up comparing the current practice against the projection method, which is described in **chapter 4**. It was investigated whether the innovation can lead to more correctly identified perforator locations and less operation time spent on dissecting the free skin flap compared to current practice. In total 60 patients were included and randomly assigned to either the control (n=27) or the projection method group (n=33). The main outcomes of this study were significant: intraoperative flap harvest time is decreased by 19 minutes using the projection method (155 ± 7 vs 136 ± 7 minutes, p=0.012) compared to the Doppler US control group when using the projection method. Furthermore, it proved to be more accurate in predicting perforator locations: 61.7% ± 7.3% success rate versus 41.2 ± 8.2% (p=0.020).

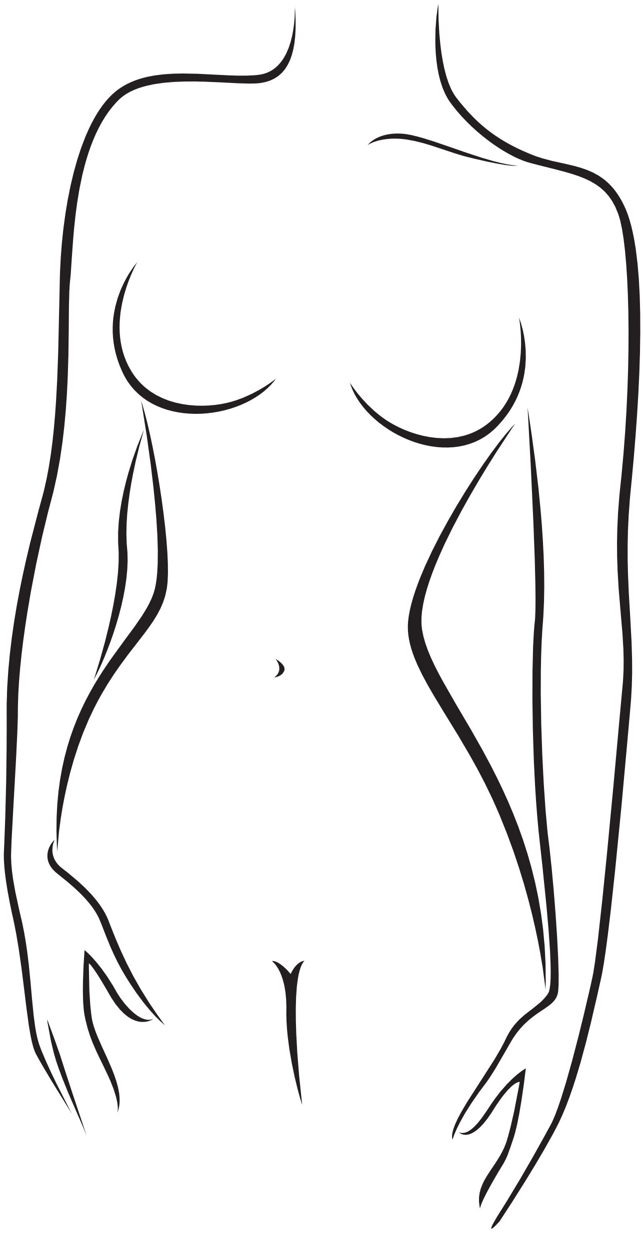
As the concept of projecting anatomical information onto the patient proved successful, more applications were explored. For women suffering from lymph edema in the upper extremity as a result of breast-cancer surgical therapies, an autologous lymph node flap from the inguinal area can be included into the DIEP flap. As the lymph nodes are hidden in the subcutaneous fat, it is useful to provide preoperative insight into their locations to minimize the total dissection area. **Chapter 5** covers the pilot study that elaborated the virtual 3D flap planning by the addition of lymph node locations and determining the accuracy of such projection. In a total of 10 patients, the preoperatively indicated lymph nodes were found intraoperatively within a one centimeter radius of the marked locations on the skin.  Surgeons reported having to dissect less tissue to find the inguinal lymph nodes, suggesting the post-operative donor site morbidity may be decreased using this technique.

**Chapter 6** describes the investigation of combining the imaging-modalities 3D stereophotography and CTA in order to improve breast reconstruction outcome. It was hypothesized that preoperative breast volume and donor site tissue volume could be planned and projected preoperatively onto the patient's abdomen to gain insight into the optimal flap volume to be harvested. By elaborating the virtual DIEP flap planning with flap delineations, we found that it is possible to harvest approximately the same preoperatively planned and projected flap volume intraoperatively. This can be considered a first step  to standardly achieve symmetric breast volumes in DIEP flap breast reconstructions.

Whereas the method described in previous chapter provided aid in selecting the flap volume for breast reconstructions, **chapter 7** shows how 3D printing techniques can be used for providing insight in the volume and shape of the reconstructed breast. In cases of unilateral reconstruction, the unaffected contralateral breast can be mirrored virtually in 3D based on stereophotogrammetry. In bilateral cases, it may aid in obtaining symmetric breast reconstructions. After 3D printing, the harvested flap can be placed inside the mould in such a manner that the flap adopts to the contralateral breast shape. Although this method has its limitations, it can support the operating surgeon in intra-operative decision making in patients with sufficient donor site tissue at low costs.

# CHAPTER 10

## Summary in Dutch



Bij een deep inferior epigastric artery perforator (DIEP) lap borst reconstructie wordt een vrije weefsellap bestaande uit vetweefsel, huid en aanvoerende bloedvaten, getransplanteerd van de buik naar de borst. De perforerende bloedvaten zijn enkele millimeters in doorsnee en van groot belang voor de overleving van de DIEP lap. Hierom worden deze zogenaamde perforatoren pre-operatief geïdentificeerd om te voorkomen dat deze per abuis worden doorgenomen tijdens de ingreep. Met Doppler ultrageluid of computer tomography angiography (CTA) kunnen deze bloedvaten in kaart worden gebracht. Echter, wanneer deze bloedvaten door CTA worden aangemerkt, is dit alleen zichtbaar op het computerscherm, waarvoor een eenvoudige methode nodig was om dit eenvoudig op de patiënt over te brengen. De explorerende studie zoals beschreven in **hoofdstuk 2** is opgezet om de hypothese te testen dat door middel van projectie een computer gegenereerde planning op de patiënt kan worden afgebeeld. Door gebruik te maken van een consumenten pico video projector bleek het mogelijk om de planning op de patiënt weer te geven. Om te zorgen dat de vergroting en rotatie van het beeld correct was, werd ter verificatie een liniaal geplaatst op de buik van de patiënt. Het geprojecteerde beeld werd overgetrokken met een markeerstift, en gecontroleerd met Doppler. Om een gouden standaard te krijgen voor de perforator locaties werden intraoperatieve metingen verricht waarmee de preoperatief geprojecteerde locaties werden vergeleken. Deze rudimentaire opzet bevestigde de hypothese dat projecties een significante meerwaarde kunnen geven in het lokaliseren van de perforatoren.

Gezien het eenvoudige prototype verdere ontwikkeling nodig had voordat het gebruikt kon worden in de klinische praktijk, werd de potentiële toegevoegde waarde van deze innovatie verder onderzocht voordat deze de ontwikkeling en onderzoeksfase in gaat. In **hoofdstuk 3** beschrijft hoe een mathematisch model van een bilaterale DIEP lap borst reconstructie werd gecreëerd, welke de totale ruimte tot verbetering in financiële termen (headroom analyse) kon berekenen, alsmede verschillende implicaties (scenario analyse) en keuzes bij verschillende uitkomsten en afkapwaarden (threshold analyse). Het model informeerde dat er ruimte tot verbetering was bij bilaterale DIEP lap borstreconstructies, ter waarde van €889 euro. Verdere modellering liet zien dat wanneer operatietijden met 15 minuten en complicaties met 50% werd verminderd, de innovatie nog steeds kosteneffectief was bij €671 per patiënt.

Om de echte impact te onderzoeken in de kliniek, werd er een single-center randomized controlled trial opgezet welke de huidige praktijk tegen de projectie methode afzet, beschreven in **hoofdstuk 4**. Het werd onderzocht of de innovatie tot meer correct geidentificieerde perforator locaties leidde, en minder tijd werd gespendeerd aan het vrijprepareren van de vrije weefsel lap, vergeleken met de huidige praktijk. In totaal werden 60 patiënten geïncludeerd en willekeurig ingedeeld in de controle groep (n=27) of de projectie methode groep (n=33). De eindresultaten van deze studie waren significant; de tijd gespendeerd aan het oogsten van de lap werd door de projectie manier verminderd met 19 minuten (155 ± 7 tegen 136 ± 7 minuten, p=0.012) vergeleken met de Doppler controle groep. Verder was deze nieuwe manier ook nauwkeuriger in het voorspellen van de perforator locaties; 61.7% ± 7.3% succes ratio tegen 41.2 ± 8.2% (p=0.020).

Toen het concept van het projecteren van anatomische informatie op de patiënt succesvol bleek werden meer toepassingen verkend. Vrouwen met lymfeoedeem in de bovenste extremiteiten als gevolg van borstkanker therapieën, kunnen worden geholpen door het toevoegen van een lichaamseigen lymfeklier lap vanuit de lies aan de DIEP lap borstreconstructie. Gezien de lymfeklieren verstopt liggen in het onderhuidse vetweefsel is het nuttig om de locaties hiervan preoperatief weer te geven om het totale dissectie gebied zo klein mogelijk te houden. **Hoofdstuk 5** omvat een pilot study om de virtuele 3D lap planning uit te breiden met de lymfeklier locaties, en de nauwkeurigheid hiervan te bepalen. Bij de geïncludeerde 10 patiënten werden de preoperatief aangeduide lymfeklieren intraoperatief binnen een straal van 1 cm van de markeringen op de huid gevonden. Chirurgen rapporteerden dat minder weefsel hoefde te worden vrijgeprepareerd om de lymfeklieren te vinden, waardoor er wellicht minder post-operatieve complicaties in het donorgebied zullen ontstaan door deze techniek.

In de inhoud van **hoofdstuk 6** wordt de combinatie van beeldvormende modaliteiten 3D stereofotografie en computer tomography angiography onderzocht om de uitkomst van borstreconstructies te verbeteren. Er werd gesteld dat preoperatief borstvolume en donor volume preoperatief gepland en geprojecteerd kon worden op de buik van de patiënt, om op die manier inzicht te krijgen in de optimale lap grootte om vrij te prepareren. Door de virtuele DIEP lap planning uit te breiden met de totale lap aftekening, lieten we in kleine aantallen zien dat het mogelijk is om ongeveer dezelfde hoeveelheid preoperatief en geprojecteerd volume intraoperatief te oogsten. Dit is een eerste stap om consequent symmetrische borstvolumes te bereiken in DIEP flap borstreconstructies.

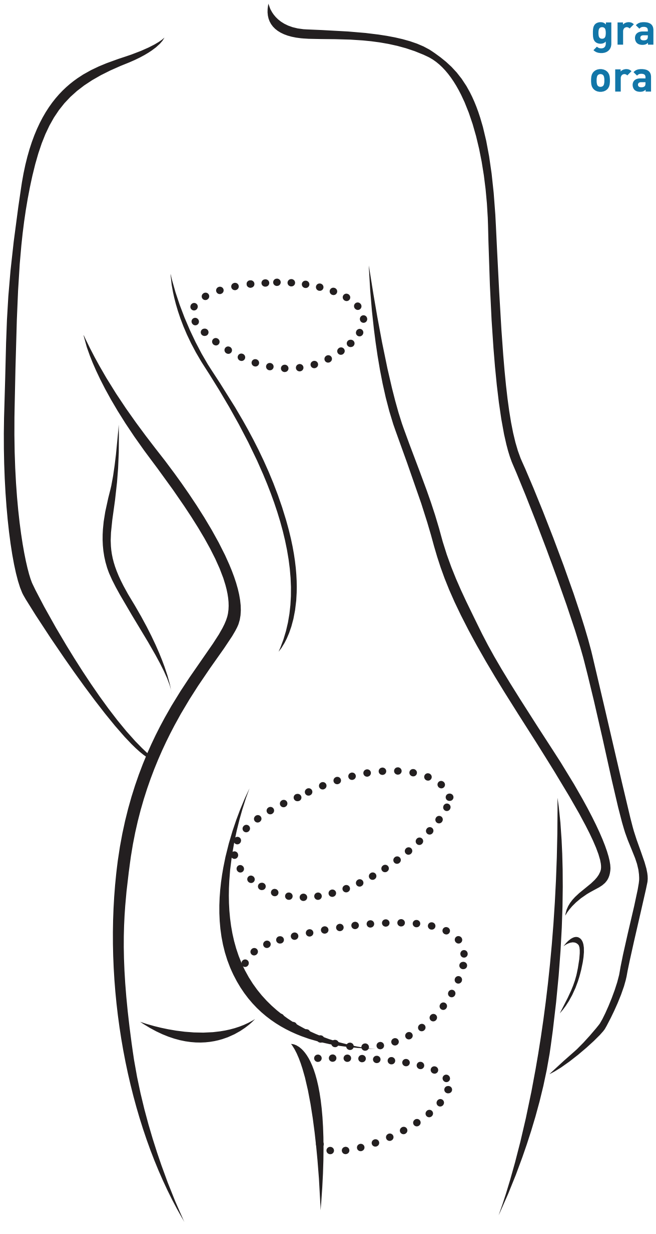
Daar de methode beschreven in het vorige hoofdstuk hulp biedt bij het selecteren van het lapvolume voor borstconstructies, toont **hoofdstuk 7** hoe 3D-printtechnieken kunnen worden gebruikt om inzicht te geven in de vorm en volume van de gereconstrueerde borst. In geval van eenzijdige borstreconstructie kan de onaangedane contralaterale borst op basis van stereofotogrammetrie in 3D worden gespiegeld. In het geval van een dubbelzijdige reconstructie kan deze dienen voor het verkrijgen van symmetrische borstvolumes. Na het 3D-printen kan de geoogste flap zo geplaatst worden dat de lap de contralaterale borstvorm overneemt. Hoewel deze methode zijn beperkingen heeft, kan het de opererende chirurg ondersteunen bij intraoperatieve besluitvorming bij patiënten met voldoende donorweefsel tegen lage kosten.

# APPENDICES

Dankwoord

Curriculum vitae

Publications, patents, grants, poster and oral presentations



# DANKWOORD

Dit proefschrift is ontstaan dankzij de velen die hieraan hebben meegewerkt. Hopelijk vergeet ik niemand?! Anders: mijn oprechte excuses!

Graag start ik bij de het bedanken van alle **patiënten** die hebben willen deelnemen aan de wetenschappelijke studies. Borstkanker en de behandeling daaromheen is een zwaar traject, met een borstreconstructie als afsluitend hoofdstuk. Ik heb dan ook veel respect voor iedereen die zich hier doorheen heeft weten te worstelen. En dan ook nog mee willen doen aan een wetenschappelijk onderzoek... Hartelijk bedankt!

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Leden van de manuscriptcommissie; **prof. dr. S. J. Bergé**, **prof. dr. R. P. H. Veth** en **prof. dr. R. R. W. J. van der Hulst**, mijn dank is groot voor het kritisch doornemen van deze dissertatie. Ook de vlotte acceptatie tot zitting in de commissie waardeer ik ten zeerste.

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Heuj **Arico**, dank voor de vele uren overleg over onderzoeksvoorstellen en de plezierige samenwerking tot dusver. Jouw proefschrift komt er vast ook snel, en help graag eraan mee!
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Beste mede-onderzoekers van de interventieradiologie, beste **Marja** en **Maarten**. Jullie suggesties rondom onderzoeksopzet en artikelen waren zeer leerzaam en leidden tot mijn eerste publicatie. Bedankt!

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Beste medewerkers van de **Valorisatie**, en met name **Frank**, dank voor de inzet om de gepresenteerde techniek in dit proefschrift tot een ingediende patentaanvraag te laten komen en plannen te schetsen voor de andere toekomstige innovaties. De onlangs toegekende subsidieaanvraag is de volgende stap waarmee we er mee verder kunnen gaan op zeer korte termijn!

Dag **Maroeska**, **Janneke** en **Jeroen**. Hartelijk dank voor al jullie hulp bij het onderzoek naar de kosteneffectiviteit. Jullie hebben me een zeer leerzame ervaring meegegeven welke nog geregeld van pas gaat komen! Ik kijk uit naar toekomstige samenwerkingen.

Moiii **Joep**, paranimf! Als een van mijn beste vrienden mag je niet ontbreken bij deze ceremonie. Doch dit een ere taak betreft weet ik zeker dat je inhoudelijk ook je steentje kan bijdragen tijdens de verdediging. Bedankt voor het afreizen uit het hoge noorden... direct maar een carbage run eraan vast knopen?

Hey broer*tje* en paranimf **Marijn**. Fijn dat je deel uit maakt van het bereiken van deze mijlpaal. Het is super om de wederzijdse interesse voor techniek en ondernemen met elkaar te kunnen delen. We zijn duidelijk uit hetzelfde hout gesneden. Het zal me niks verbazen als wij ergens in de toekomst nog samen een nevenprojectje erbij gaan starten...

Lieve **Philo**! Waar we in het begin onze dates om de 'projectie-avonden' heen moesten plannen, kunnen we nu zo vaak samen zijn als we willen. Tis heerlijk om met zo'n liefdevolle knuffel thuis verwelkomd te komen. Thx voor de nodige balans tussen werk en relaxen. Kusje!

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Last but absolutely not least, **mijn ouders**. Pa en mam. Jullie wisten al vanaf jonge leeftijd dat ik de medische tak ging op zoeken, en hebben me daar ook volledig in gesteund. Bedankt dekt de lading niet. Maargoed, bij gebrek aan een beter woord... Oneindig bedankt voor alle liefde en de mogelijkheid dat ik überhaupt heb kunnen studeren. Zonder jullie onvoorwaardelijke steun zou ik hier nu niet geweest. Dus, dit proefschrift is voor jullie!

# CURRICULUM VITAE

Stefan Hummelink werd geboren op 15 november 1988 in Veldhoven. In 2007 werd het VWO diploma gehaald op het Sondervick College te Veldhoven, waarna aansluitend de studie Technische Geneeskunde werd gestart aan de Universiteit Twente te Enschede. Vanaf zijn tweede jaar tot en met het einde van de studie was hij betrokken als student-assistent bij meer dan tien verschillende vakken. In 2013 startte hij zijn bedrijf GuitarFX, gespecialiseerd in- en verkoop, modificaties en reparaties van tweedehandse gitaareffectpedalen. Na het afstuderen aan de Universiteit Twente in de zomer van 2014 kon gecontinueerd worden met zijn werkzaamheden in het Radboudumc bij de afdeling radiologie en de afdeling plastische chirurgie. In deze periode werd onderzoek verricht naar technologieën rondom autologe borstreconstructieve ingrepen, wat resulteerde in een toegekend patent, en meerdere wetenschappelijke publicaties welke te lezen zijn in dit proefschrift. Daarnaast is hij sinds 2017 onderzoekscoördinator van de afdeling plastische chirurgie en heeft hij een twee jaar durend fellowshiptraject vanuit technische geneeskunde op gebied van innovaties bij borstreconstructies toebedeeld gekregen.

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# PUBLICATIONS, PATENTS, GRANTS, POSTER AND ORAL PRESENTATIONS

## Publications

**Preliminary results using a newly developed projection method to visualize vascular anatomy prior to DIEP flap breast reconstruction**
*S. Hummelink, M. Hameeteman, Y. L. Hoogeveen, C. H. Slump, D. J. O. Ulrich, L. J. Schultze Kool*
*Journal of Plastic and Reconstructive Aesthetic Surgery. 2015;68(3):390-4.*
*doi: 10.1016/j.bjps.2014.11.006*

**The merits of decision modelling in the earliest stages of the IDEAL framework - an innovative case in bilateral breast reconstruction**
*S. Hummelink, J. G. W. Gerrits, L. J. Schultze Kool, D. J. O. Ulrich, M. M. Rovers, J. P. C. Grutters*
*Journal of Plastic and Reconstructive Aesthetic Surgery. 2017; 2017;70(12):1696-1701*
*doi: 10.1016/j.bjps.2017.07.011*

**The benefits of using innovative imaging techniques: A randomized controlled trial in breast reconstructive surgery**
*S. Hummelink, Y. L. Hoogeveen, L. J. Schultze Kool, D. J. O. Ulrich*
*JAMA Surgery (2018); submitted*

**Displaying inguinal lymph nodes prior to transplantation in a deep inferior epigastric perforator flap breast reconstruction using an innovative projection method**
*S. Hummelink, L. J. Schultze Kool, D. J. O. Ulrich*
*Journal of Plastic and Reconstructive Aesthetic Surgery. 2016;69(3):376-80.*
*doi: 10.1016/j.bjps.2015.10.041*

**An innovative method of planning and displaying flap volume delineations additional to perforator mapping to achieve symmetric breast volumes in DIEP flap breast reconstructions**
*S. Hummelink, A. C. Verhulst, T. J. J. Maal, Y. L. Hoogeveen, L. J. Schultze Kool, D. J. O. Ulrich*
*Journal of Plastic and Reconstructive Aesthetic Surgery. 2017;70(7):871-875.*
*doi: 10.1016/j.bjps.2017.04.008.*

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**Clinical experience using patient-specific 3D printed moulds in autologous breast reconstruction**
*A. C. Verhulst, S. Hummelink, T. J. J. Maal, D. J. O Ulrich*
*Journal of Reconstructive Microsurgery (2018); submitted*

## Patent

**Anatomical image projection system**

*Filed March 2015 under WO2015/135985A1*

Patent pending - Europe

Patent granted - United States of America (June 2017).

## Grant

**STW: Stichting voor de Technische Wetenschappen - Demonstrator Grant: Anatomy Projector** *Awarded July 2017*

## Oral and poster presentations

**ISSiS: International Society for Simulation Surgery, 2015, Seoul, South-Korea**

*Oral presentation: Virtual Planning of DIEP Flap Breast Reconstructions based on Computed Tomography Angiography*

**CIRSE: Cardiovascular and Interventional Radiological Society of Europe, 2015, Lisbon, Portugal**

*Poster presentation: Preliminary results using a newly developed projection method to visualize vascular anatomy prior to DIEP flap breast reconstruction*

**SEOHS: Symposium Experimenteel Onderzoek Heelkundige Specialismen, 2015, Leiden, the Netherlands**

*Poster presentation: Displaying inguinal lymph nodes prior to transplantation in a DIEP flap breast reconstruction using an innovative projection method*

**ECR: European Congress of Radiology, 2016, Vienna, Austria**

*Oral presentation: Displaying inguinal lymph nodes prior to transplantation in a DIEP flap breast reconstruction using an innovative projection method*

**NVPC: Nederlandse Vereniging voor Plastische Chirurgie, 2016, Eindhoven, the Netherlands**

*Oral presentation: Opzetten van een mammareconstructie database ter verbetering van uitkomstmaten en (inter)nationale kwaliteitsvergelijking*

**EURAPS: European Association of Plastic Surgeons, 2016, Brussels, Belgium**

*Oral presentation: Displaying inguinal lymph nodes prior to transplantation in a DIEP flap breast reconstruction using an innovative projection method*

**SEOHS: Symposium Experimenteel Onderzoek Heelkundige Specialismen, 2016, Utrecht, the Netherlands**

*Oral presentation: Het totale DIEP lapvolume plannen en projecteren op de patiënt om symmetrische borsvolumes te realiseren*

**STW: Stichting voor de Technische Wetenschappen - Demonstrator Grant, 2017, Utrecht, the Netherlands**

*Oral presentation: Anatomy Projector -- Subsidy granted June 2017*

**EURAPS: European Association of Plastic Surgeons, 2017, Pisa, Italy**

*Oral presentation: An innovative method of planning and displaying flap volume delineations additional to perforator mapping in DIEP flap breast reconstructions*

**ESSR: European Society for Surgical Research, 2017, Amsterdam, the Netherlands**
*Oral presentation: Visualizing vascular anatomy prior to DIEP flap breast reconstructions using an innovative projection method*

**London Breast Meeting, 2017, London, United Kingdom**
*Oral presentation: An innovative method of planning and displaying flap volume delineations additional to perforator mapping in DIEP flap breast reconstructions -- Best paper awards: 2nd place*

**NVPC: Nederlandse Vereniging voor Plastische Chirurgie, 2017, Hengelo, the Netherlands**
*Oral presentation: Het projecteren van virtuele planning voorafgaand aan DIEP lap borstreconstructie middels een innovatieve methode: Een randomized controlled trial*

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